DEPARTMENT OF SCIENTIFIC EVALUATION OF REGULATED PRODUCTS

Ref. MT/TM/sda (2021) – OC-2021-24995935

Natacha Cingotti
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On behalf of Alerte des Médecins sur les Pesticides and Générations Futures

Re: Additional questions regarding the peer-review status of several pesticide active substances, including endocrine disruption assessment

Ref.: Your letter dated 16 June 2021

Dear Ms Cingotti,

Thank you for your follow up letter sent on behalf of *HEAL*, *AMLP* and *Générations Futures*, raising additional questions following the clarifications provided by EFSA concerning the status of the peer-review of several pesticide active substances, including endocrine disruption assessment on: **Cyprodinil, Fenbuconazole, Mepanipyrim, Spinosad, Ziram** and **Pyrimethanil**.

We acknowledge your concerns raised as regards the timelines of the evaluation process for five of these substances, impacted by application of the 'clock stop' provisions as laid down in Commission Regulation (EU) No 2018/1659 in view of the implementation of the new scientific criteria for the determination of endocrine disrupting properties.

According to the applicable legislation, where, based on the information available to the peer review, it is already possible to conclude that the substance meets the criteria for endocrine disruption, a clock stop of maximum **3 months** is permitted for applicants to supply any additional information[1], thereby keeping the extension of the renewal process to a minimum, whilst the long term clock stop of up to **30 months** may be applied in case the data package is incomplete preventing a conclusion to be drawn on the endocrine properties[2].

In the latter case, the '*Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009*' recommends a tiered assessment strategy, starting from generation of level 2/3 studies as appropriate to complete the data package. However, in case of positive result/s based on these tests for

[1] See Article 13(3a), third subparagraph, of Commission 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 Text with EEA relevance (OJ L 252, 19.9.2012, p. 26), as amended by Commission Regulation (EU) 2018/1659 of 7 November 2018 amending Implementing Regulation (EU) No 844/2012 in view of the scientific criteria for the determination of endocrine disrupting properties introduced by Regulation (EU) 2018/605 (OJ L 278, 8.11.2018, p. 3).

[2] See Article 13(3a), first subparagraph, of Commission Regulation (EU) No 844/2012.

at least one modality (e.g. T (thyroid)- and/or EAS (oestrogen, androgen and steroidogenesis) modalities), additional higher tier testing would be needed in order to further investigate the adversity. Following EFSA's recommendations on the tests to be performed, the decision on the final testing strategy and the corresponding timeline falls under the applicants' responsibility.

In the EFSA letter of request for additional information, applicants are requested to confirm the timelines needed for submission of the data to be generated depending on their chosen testing strategy, taking into account the legal requirement that **the period ultimately set for the submission of additional information must be justified to the type of information which will be submitted**. Furthermore, applicants are given the possibility to change their initial testing strategy and the indicated submission date during the 'clock stop' pending the outcome of the commissioned studies, by providing a justification of the revised timeline for the alternative testing strategy.

The maximum amount of time (30 months) is not granted by EFSA systematically, but it is based on the considerations received from the applicants following their decision on the number and nature of the chosen tests to be commissioned, together with their justification for the associated time needed.

For the above mentioned five substances, overall the EFSA requests recommended a tiered assessment strategy in line with the '*Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009'*, requiring a comprehensive set of data to be generated, comprising, in the majority of the cases, relevant level 2/3 tests and higher tier testing as appropriate, including tests for both humans and non-target organisms.

As a basis for the estimation of the time needed, **Annex 1 to the EFSA's Administrative guidance for the processing of applications for regulated products**[3] (see in Annex to this letter an extract with the list of studies on endocrine properties for easier reference) provides indicative timelines for applicants for submitting additional information to EFSA during the risk assessment. This shows that the indicative timeframe for submission of tests following request for additional studies on endocrine properties ranges between 9 – 30 months, with the majority of the tests falling between 19 – 24 months, excluding aspects such as the time needed for the availability of testing facilities. Laboratory capacity to perform the tests needed appears to be often a limiting factor that applicants are confronted with and that may add significant additional time to the actual total time needed for initiating, conducting, reporting and assessing the required studies. Such considerations are taken into account by the applicants when deciding on their final testing strategy along with the associated timeline needed.

Likewise, for the concerned substances, the following reasonings were provided:

- the standard timeframe for the proposed complex studies;

[3] EFSA (European Food Safety Authority), 2019. Administrative guidance for the processing of applications for regulated products. EFSA supporting publication 2018:EN-1362. 19 pp. doi:10.2903/sp.efsa.2018.EN-1362.

- the limited availability of time slots in laboratories and/or adequate contract research organizations for the conduct of such type of studies;
- significant lead time for the required assays to be performed / additional waiting time due to substantial increase in the demand for some studies following publication of the Endocrine Criteria and Technical Guidance to assess these;
- the scientific assessment and interpretation of the new results, along with the need to update the supplementary dossier (with updated Appendix E) which are required to be completed in the given timeline.

EFSA acknowledges the regulatory challenges which risk managers are facing due to the current lack of data about endocrine disrupting properties, preventing them from taking informed decision on the renewal. Actually, for 2 of the respective substances (spinosad, mepanipyrim), the EFSA Conclusions following the renewal process were already made available before the entry into force of the new endocrine criteria; nevertheless, no decision could be taken within the Standing Committee for Plants Animals Food and Feed (PAFF Committee) as to whether the respective active substance is or not an endocrine disruptor. This is why the Commission mandated EFSA to reassess the information in accordance with the new criteria.

EFSA also acknowledges that the long term 'clock stops', required to permit generation of adequate data and enable a conclusion, significantly prolong the overall timeline of the renewal process, which may require consideration by the Commission of the extension of the approval periods for certain substances. In this context, EFSA makes sure to promptly inform the Commission in case the scientific assessment points out that any of the cut-off criteria might be met or critical concerns are identified during the peer review. In particular, EFSA regularly informs risk managers about the status of substances under clock stop, as well as the outcome of the peer review expert meetings, including eventual concerns identified. This to allow the Commission, where necessary to safeguard human and animal health and the environment, to take appropriate regulatory action even prior to the completion of the peer review, preventing, when appropriate, that such substances remain on the market.

We trust your understanding in this challenging situation, on one hand serving the needs of risk managers to make informed regulatory decisions on the basis of the conclusions reached following generation of adequate data, whilst ensuring protection of human and animal health and the environment despite the resulting increased time of the renewal process.

In addition, we take note of your suggestion according to which the Transparency Regulation[4] should be interpreted as requiring that any data submitted after 27 March 2021 for the purpose of fulfilling additional data requirements, shall be published following the provisions of this Regulation.

[4] Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain and amending Regulations (EC) No 178/2002, (EC) No 1829/2003, (EC) No 1831/2003, (EC) No 2065/2003, (EC) No 1935/2004, (EC) No 1331/2008, (EC) No 1107/2009, (EU) 2015/2283 and Directive 2001/18/EC (OJ L 231, 6.9.2019, p. 1 28).

In accordance with Article 38(1)(c) of Regulation (EC) No 178/2002[5] and Article 10 of Regulation (EC) No 1107/2009, as both amended by the Transparency Regulation, EFSA shall make available to the public all scientific data, studies and other information supporting an admissible application, including any supplementary information supplied by the applicant. Nevertheless, Article 10(1) of the Transparency Regulation provides that *'This Regulation shall not apply to applications under Union law as well as requests for scientific outputs submitted to the Authority before 27 March 2021'*. The term 'applications' is intended to cover the entire application life-cycle, including the submission of additional data within the same application process[6]. Since the applications for the above mentioned five substances were submitted before 27 March 2021, or the new mandates were addressed to EFSA before that date, the Transparency Regulation is not yet applicable, including the afore-mentioned provisions on public disclosure.

It is also worth noting that the provisions of the Transparency Regulation that are pertinent for the renewal procedure for active substances provided for in Regulation (EC) No 1107/2009 are implemented in Commission Implementing Regulation (EU) 2020/1740[7]. In accordance with recitals (17) and (18) and Article 17 thereof, this Regulation shall apply with respect to the renewal of the approval of active substances for which the approval period ends on or after 27 March 2024. While Regulation (EU) No 844/2012 will continue to apply to active substances whose approval period expires before 27 March 2024, which is the case of the above mentioned five substances.

We trust that the above clarifications may prove to be helpful and we appreciate your understanding and support in this important matter.

Yours sincerely,

Manuela Tiramani

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Encl: Annex

[5] Regulation (EC) No 178/2002 of the European Parliament and Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety (OJ L 31, 1.2.2002, p. 1).

[6] See also the Questions and Answers on EFSA Practical Arrangements, in particular Question B.2.

[7] Commission Implementing Regulation (EU) 2020/1740 of 20 November 2020 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, and repealing Commission Implementing Regulation (EU) No 844/2012 (OJ L 392, 23.11.2020, p. 20).

Annex - Indicative timelines for submitting additional information

Contents	EFSA request for Additional or Supplementary Information	OECD Test Guidelines	Indicative Timelines for submitting information to EFSA
Endocrine disrupting properties	21-day Fish Assay: A Short-Term Screening for Oestrogenic and Androgenic Activity, and Aromatase Inhibition	230	19 months
Endocrine disrupting properties	Amphibian Metamorphosis Assay	231	19 months
Endocrine disrupting properties	Androgenised female stickleback screen	148	19 months
Endocrine disrupting properties	BG1Luc Estrogen Receptor Transactivation Test Method for Identifying Estrogen Receptor Agonists and Antagonists	457	9 months
Endocrine disrupting properties	Extended one generation reproductive toxicity study	443	24 months
Endocrine disrupting properties	Fish life cycle toxicity (OCSPP 890.2301)		30 months
Endocrine disrupting properties	Fish Sexual Development Test	234	19 months
Endocrine disrupting properties	Fish Short Term Reproduction Assay	229	19 months
Endocrine disrupting properties	Hershberger Bioassay in Rats, A Short-term Screening Assay for (Anti)Androgenic Properties	441	20 months
Endocrine disrupting properties	Larval Amphibian Growth and Development Test	241	27 months
Endocrine disrupting properties	Medaka Extended One-Generation Reproduction Test	240	28 months
Endocrine disrupting properties	OCSPP Guideline 890.1450: Pubertal Development and Thyroid Function in Intact Juvenile/Peripubertal Female Rats Assay		23 months
Endocrine disrupting properties	OCSPP Guideline 890.1500: Pubertal Development and Thyroid Function in Intact Juvenile/Peripubertal Male Rats Assay		23 months

Contents	EFSA request for Additional or Supplementary Information	OECD Test Guidelines	Indicative Timelines for submitting information to EFSA
Endocrine disrupting properties	Performance-Based Test Guideline for Human Recombinant Estrogen Receptor (hrER) In Vitro Assays to Detect Chemicals with ER Binding Affinity	493	9 months
Endocrine disrupting properties	Reproduction/ Developmental Toxicity Screening Test	421	15 months
Endocrine disrupting properties	Stably transfected human androgen receptor activation assay for detection of androgenic agonist and antagonist activity of chemicals	458	9 months
Endocrine disrupting properties	Stably Transfected Human Estrogen Receptor-alpha Transcriptional Activation Assay for Detection of Estrogenic Agonist-Activity of Chemicals (update from July 2016)	455	9 months
Endocrine disrupting properties	Steroidogenesis (Human cell line H295R)	456	9 months
Endocrine disrupting properties	Two generation reproduction toxicity study	416	24 months
Endocrine disrupting properties	Uterotrophic Bioassay in Rodents A short-term screening test for oestrogenic properties	440	20 months