Chlorpyrifos
SANTE/11938/2019 Rev 1
6 December 2019

FINAL Renewal report for the active substance chlorpyrifos
finalised in the Standing Committee on Plants, Animals, Food and Feed
at its meeting on 6 December 2019
in view of the non-renewal of the approval of chlorpyrifos as an active substance
in accordance with Regulation (EC) No 1107/2009

1. Procedure followed for the re-evaluation process

This renewal report has been established as a result of the evaluation of chlorpyrifos (also known as chlorpyrifos-ethyl), in accordance with Regulation (EC) No 1107/2009 and Commission Implementing Regulation (EU) No 844/2012 following the submission of an application to renew the approval of this active substance expiring in January 2020.


Separate applications for the renewal of the approval of chlorpyrifos were submitted by the Chlorpyrifos Task Force (comprising Dow AgroSciences Limited and Adama Agricultural Solutions Limited), and by SAPEC Agro S.A. in accordance with Article 1 of Regulation No 844/2012.

The approval period of chlorpyrifos, originally expiring on 30 June 2016, has been extended three times in accordance with Article 17 of Regulation (EC) No 1107/2009:

- Commission Implementing Regulation (EU) No 762/2013 extended until 31 January 2018 the period of approval of chlorpyrifos as part of the organisation of the AIR3 renewal programme.

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1 Renewal Report established in accordance with Art. 14 of Regulation (EU) No 844/2012; does not necessarily represent the views of the European Commission.
• Commission Implementing Regulation No 2018/84\textsuperscript{8} extended until 31 January 2019 the period of approval of chlorpyrifos to allow the completion of its review due to delays in the scientific assessment process.

• Commission Implementing Regulation (EU) 2018/1796\textsuperscript{9} extended until 31 January 2020 the period of approval of chlorpyrifos to allow the completion of its review due to delays in the scientific assessment process.

Commission Implementing Regulation (EU) No 686/2012\textsuperscript{10} designated the rapporteur Member States and the co-rapporteur Member States which had to submit the relevant renewal assessment reports and recommendations to the European Food Safety Authority (EFSA), for substances whose approval expired on or before 31 December 2018.

For chlorpyrifos the rapporteur Member State was Spain and the co-rapporteur Member State was Poland.

On 3 July 2017, Spain sent to the Commission and EFSA a draft renewal assessment report (RAR). This RAR included a recommendation concerning the decision to be taken with regards to the renewal of the approval of chlorpyrifos for the supported uses.

In accordance with Article 13 of Implementing Regulation (EU) No 844/2012, EFSA organised an intensive consultation of technical experts from Member States, to review the RAR and the comments received thereon (peer review). EFSA also launched a public consultation on the RAR.

In April 2019, EFSA convened an expert meeting to discuss certain elements related to mammalian toxicology and human health.

The results of the expert discussions led the Commission to send, on 1 July 2019, a mandate to EFSA asking for a statement on the main findings of the assessment related to human health, and to indicate whether chlorpyrifos can be expected to meet the approval criteria which are applicable to human health as laid down in Article 4 of Regulation (EC) No 1107/2009.

On 31 July 2019, EFSA sent to the Commission a statement\textsuperscript{11} on the outcomes of the risk assessment for human health for chlorpyrifos, in which it took the view that the active substance cannot be expected to meet the approval criteria.

According to the provisions of Article 14 of Implementing Regulation (EU) No 844/2012, the Commission referred a draft renewal report to the Standing Committee on Plants, Animals, Food and Feed, for examination on 22 October 2019. The draft renewal report was finalised in the meeting of the Standing Committee on 6 December 2019.

The present renewal report contains the conclusions of the final examination by the Standing Committee. Given the importance of the statement of EFSA and the RAR these documents are also considered to be part of this renewal report.

\textsuperscript{7} To ensure that ‘new’ data requirements under Commission Implementing Regulations (EU) No 283/2013 and 284/2013 would apply to the dossiers and to distribute work in a more manageable fashion for EFSA.


\textsuperscript{10} OJ L 200, 27.7.2012, p. 5.

2. Purposes of this renewal report

This renewal report, including the documents referred to above, has been developed and finalised in support of Commission Implementing Regulation (EU) 2020/18\textsuperscript{12} concerning the non-renewal of approval of chlorpyrifos as an active substance under Regulation (EC) No 1107/2009.

This renewal report will be made available to the public.

The information in this renewal report is, at least partly, based on information, which is confidential and/or protected under the provisions of Regulation (EC) No 1107/2009. It is therefore recommended that this renewal report would not be accepted to support any registration outside the context of that Regulation, e.g. in third countries, for which the applicant has not demonstrated to have regulatory access to the information on which this renewal report is based.


The overall conclusion of the evaluation in relation to impacts on human health, based on the information available and the proposed conditions of use, is that:

- the information available indicates that the approval criteria as set out in Article 4(1) to (3) of Regulation (EC) No 1107/2009 are not satisfied as concerns were identified with regards to:

  - The genotoxic potential of chlorpyrifos, which can not be ruled out based on the information available - positive findings were found in an \textit{in vitro} chromosome aberration study and two \textit{in vitro} unscheduled DNA synthesis assays; \textit{in vivo} positive findings were found in open literature on chromosome aberration and on DNA damage caused through oxidative stress or by topoisomerase II inhibition which is considered a molecular initiating event for infant leukaemia. Consequently, health based reference values cannot be established for chlorpyrifos and the dietary and non-dietary risk assessments cannot be conducted.

  - Developmental neurotoxicity (DNT) - effects were observed in the available study on developmental neurotoxicity in rats (adverse effects were seen at the lowest dose tested in rats and a no observed adverse effects level ‘NOAEL’ could not be established) and epidemiological evidence exists showing an association between exposure to chlorpyrifos and/or chlorpyrifos-methyl\textsuperscript{13} during development and adverse neurodevelopmental outcomes in children.

  - Based on the evidence for DNT, experts during the peer review suggested that classification of chlorpyrifos as toxic for reproduction, category 1B, H360D ‘May damage the unborn child’, in accordance with the criteria set out in Commission Regulation (EC) No 1272/2008\textsuperscript{14} would be appropriate.

\textsuperscript{13} Taking into account that the methodology used for determining exposure (measurement of the common metabolite, trichloro-pyridinol (TCP), in urine) cannot discriminate between exposure to chlorpyrifos and chlorpyrifos-methyl.
In conclusion, from the assessments made on the basis of the available information (RAR, comments thereon, EFSA statement, applicant comments on the EFSA statement and draft renewal report), no plant protection product containing the active substance chlorpyrifos is expected to satisfy the requirements laid down in Article 29(1) of Regulation (EC) No 1107/2009 and the uniform principles laid down in Regulation (EU) No 546/2011.

The approval of chlorpyrifos in accordance with Regulation (EC) No 1107/2009 should therefore not be renewed.
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Chlorpyrifos

Ventura C\(^1\), Nieto MR\(^1\), Bourguignon N\(^2\), Lux-Lantos V\(^2\), Rodriguez H\(^3\), Cao G\(^4\), Randi A\(^5\), Cocca C\(^1\), Núñez M\(^6\)

Endocrine disruptors (EDs) are compounds that interfere with hormone regulation and influence mammary carcinogenesis. We have previously demonstrated that the pesticide chlorpyrifos (CPF) acts as an ED in vitro, since it induces human breast cancer cells proliferation through estrogen receptor alpha (ER\(\alpha\)) pathway. In this work, we studied the effects of CPF at environmental doses (0.01 and 1mg/kg/day) on mammary gland, steroid hormone receptors expression and serum steroid hormone levels. It was carried out using female Sprague-Dawley 40-days-old rats exposed to the pesticide during 100 days. We observed a proliferating ductal network with a higher number of ducts and alveolar structures. We also found an increased number of benign breast diseases, such as hyperplasia and adenosis. CPF enhanced progesterone receptor (PgR) along with the proliferating cell nuclear antigen (PCNA) in epithelial ductal cells. On the other hand, the pesticide reduced the expression of co-repressors of estrogen receptor activity REA and SMRT and it decreased serum estradiol (E2), progesterone (Pg) and luteinizing hormone (LH) levels. Finally, we found a persistent decrease in LH levels among ovariectomized rats exposed to CPF. Therefore, CPF alters the endocrine balance acting as an ED in vivo. These findings warn about the harmful effects that CPF exerts on mammary gland, suggesting that this compound may act as a risk factor for breast cancer.
Pesticide chlorpyrifos acts as an endocrine disruptor in adult rats causing changes in mammary gland and hormonal balance.

Ventura C1, Nieto MR1, Bourguignon N2, Lux-Lantos V2, Rodriguez H3, Cao G1, Randi A5, Cocca C1, Núñez M1

Abstract

Endocrine disruptors (EDs) are compounds that interfere with hormone regulation and influence mammary carcinogenesis. We have previously demonstrated that the pesticide chlorpyrifos (CPF) acts as an ED in vitro, since it induces human breast cancer cells proliferation through estrogen receptor alpha (ERα) pathway. In this work, we studied the effects of CPF at environmental doses (0.01 and 1mg/kg/day) on mammary gland, steroid hormone receptors expression and serum steroid hormone levels. It was carried out using female Sprague-Dawley 40-days-old rats exposed to the pesticide during 100 days. We observed a proliferating ductal network with a higher number of ducts and alveolar structures. We also found an increased number of benign breast diseases, such as hyperplasia and adenosis. CPF enhanced progesterone receptor (PgR) along with the proliferating cell nuclear antigen (PCNA) in epithelial ductal cells. On the other hand, the pesticide reduced the expression of co-repressors of estrogen receptor activity REA and SMRT and it decreased serum estradiol (E2), progesterone (Pg) and luteinizing hormone (LH) levels. Finally, we found a persistent decrease in LH levels among ovariectomized rats exposed to CPF. Therefore, CPF alters the endocrine balance acting as an ED in vivo. These findings warn about the harmful effects that CPF exerts on mammary gland, suggesting that this compound may act as a risk factor for breast cancer.
### Search active substances

**Search term:** chlorpyrifos

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