



APPROVED: 27 September 2019

doi: 10.2903/j.efsa.2019.5866

Updated peer review concerning the risk to mammals and bees for the active substance indoxacarb

European Food Safety Authority (EFSA)

Abstract

Following the completion of the pesticides peer review process in the context of the renewal of the approval of indoxacarb in accordance with Commission Implementing Regulation (EU) No 844/2012, EFSA identified critical areas of concern in the area of ecotoxicology, however no expert discussion on that section was held during the renewal process. Following further considerations during the decision-making process, the European Commission asked EFSA to discuss the risk assessment for herbivorous mammals and the risk to bees in an expert meeting and provide a Statement on the outcome of the updated peer review. The critical areas of concern identified in the renewal process as regards the long-term risk for mammals, earthworm-eating mammals and for honeybees are retained.

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Keywords: Indoxacarb, pesticides, insecticide, ecotoxicology, risk assessment for mammals, bees

Requestor: European Commission

Question number: EFSA-Q-2019-00326

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Acknowledgments: EFSA wishes to thank the rapporteur Member State France for the support provided to this scientific output.

Suggested citation: EFSA (European Food Safety Authority), 2019. Statement on the updated peer review concerning the risk to mammals and bees for the active substance indoxacarb. *EFSA Journal* 2019;17(10):5866, 10 pp. <https://doi.org/10.2903/j.efsa.2019.5866>

ISSN: 1831-4732

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Summary

Indoxacarb is a substance covered by the third stage of the renewal programme ('AIR3') in accordance with Commission Implementing Regulation (EC) No 844/2012.

An application for renewal of the approval of indoxacarb was submitted by FMC Corporation (former DuPont de Nemours GmbH) to the rapporteur Member State (RMS), France, and the co-rapporteur Member State (co-RMS), Spain. Following the completion of the peer review, the European Food Safety Authority (EFSA) published its Conclusion on the pesticide peer review for indoxacarb on 25 January 2018 (updated on 25 July 2018). EFSA identified critical areas of concern as regards ecotoxicology; however, no expert discussion on that section was held during the peer review process.

Following further considerations by risk managers during the decision-making process, on 15 May 2019 the European Commission requested EFSA to discuss the risk assessment for herbivorous mammals and the risk to bees in an expert meeting and to provide a Statement on the outcome.

The present Statement contains the outcome of the updated peer review concerning the risk to mammals and bees for indoxacarb following the Pesticides Peer Review Experts' meeting on ecotoxicology held on 17–21 June 2019. The following conclusions are derived:

- The long-term risk remains high for small herbivorous mammals for indoxacarb for the representative uses on maize even when using the endpoint in line with the mammalian toxicology conclusion;
- A refined long-term risk assessment is still triggered, but the available refinements are not considered acceptable and therefore a high long-term risk is concluded for the representative uses on maize;
- The long-term risk for small herbivorous mammals is high also when considering only a single application in maize for separated growth stages before or after BBCH 40;
- The updated risk assessment indicates high risk for earthworm-eating mammals from secondary poisoning for the representative uses of indoxacarb on maize considering multiple applications, in accordance with the GAP table used in the EFSA Conclusion issued in 2018. The risk for earthworm-eating mammals is low when considering a single application at BBCH growth stage above and below 40, and for multiple applications at BBCH above 40; however, these uses deviate from the representative uses considered under the peer review of indoxacarb reported in the EFSA Conclusion issued in 2018;
- For adult (acute contact, acute oral and chronic) honeybees and bumble bees (acute contact and oral), high risk is concluded from exposure to indoxacarb for the treated crops for applications made up to BBCH growth stage 70 and low risk after BBCH 70 (i.e. post-flowering period), and high risk is concluded for the weeds scenarios for the representative uses on maize. The mitigations measures proposed for both scenarios are not considered acceptable.

Therefore, the critical areas of concern identified in the EFSA Conclusion issued in 2018 as regards the long-term risk for mammals, earthworm-eating mammals and for honeybees are retained.

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1. Introduction

Indoxacarb is a substance covered by the third stage of the renewal programme ('AIR3') in accordance with Commission Implementing Regulation (EC) No 844/2012.

An application for renewal of the approval of indoxacarb was submitted by FMC Corporation (former DuPont de Nemours GmbH) to the rapporteur Member State (RMS), France, and the co-rapporteur Member State (co-RMS), Spain. Following the completion of the peer review, the European Food Safety Authority (EFSA) published its Conclusion on the pesticide peer review for indoxacarb on 25 January 2018 (updated on 25 July 2018) (EFSA, 2018). EFSA identified critical areas of concern in the area of ecotoxicology; however, no expert discussion on that section was held during the peer review process.

The European Commission proceeded with the decision-making as regards indoxacarb, i.e. it consulted the applicant and Member States on the EFSA Conclusion and the draft review report prepared by the Commission as provided by the legal framework. Comments were received from the applicant on the risk assessment for herbivorous mammals and the risk to bees which were forwarded to EFSA and the RMS France. The RMS France indicated a need to discuss the long-term endpoint for mammals.

Therefore, following further considerations during the decision-making process, on 15 May 2019, by means of a mandate the European Commission requested EFSA to discuss the risk assessment for herbivorous mammals and the risk to bees in an expert meeting and to provide a Statement on the outcome.

To facilitate the expert discussions, a revised version of the pertinent sections of the renewal assessment report (RAR) was prepared by the RMS providing their preliminary considerations, which was subsequently updated with the outcome of the discussions (France, 2019).

The present Statement contains the outcome of the updated peer review concerning the risk to mammals and bees for indoxacarb following the Pesticides Peer Review Experts' meeting on ecotoxicology held on 17–21 June 2019.

All other aspects and conclusions from the peer review of the renewal process finalised by EFSA in 2018 (EFSA, 2018) remain unchanged.

A key supporting document to this Statement is the peer review report (EFSA, 2019), which is a compilation of all the documents developed during the evaluation and the assessment requested in the mandate. The peer review report comprises the following documents, in which all views expressed during the process, including minority views, where applicable, can be found:

- the comments received on the draft Statement;
- the report of the scientific consultation with Member State experts.

Given the importance of the peer review report, this document is considered as a background document to this Statement and thus is made publicly available.

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

On 15 May 2019 the European Commission requested EFSA for an updated peer review concerning the risk to mammals and bees for indoxacarb focusing on the representative uses in maize; in particular to discuss the risk assessment for herbivorous mammals and the risk to bees in an expert meeting and to provide a Statement considering the following points:

- the long-term endpoint for mammals to be used in the ecotoxicological risk assessment;
- the options for refinement of the risk to mammals as available and reported by the RMS in the revised assessment report section B-9 PPP (France, 2019);
- an assessment of the risk to herbivorous mammals for a single application of 37.5 g a.s./ha in maize (BBCH 34-77) based on the data available during the peer review and, if applicable, separated for growth stages before or after BBCH 40;
- the risk to bees including the possibility for risk mitigation measures.

For this purpose, a Statement is prepared containing the outcome of the updated peer review concerning the risk to mammals and bees for indoxacarb following the Pesticides Peer Review Experts' meeting 08 on ecotoxicology held on 17–21 June 2019.

2. Assessment

2.1. Risk assessment for mammals

2.1.1. Long-term endpoint for mammals

During the peer review of indoxacarb 150 g/L EC (emulsifiable concentrate), the no observed adverse effect level (NOAEL) from a multigeneration study with the test substance DPXJW062 (50:50 of DPX-KN128:IN-KN127) was used for carrying out the long-term risk assessment for mammals (EFSA, 2018). In order to account for the isomeric ratio of DPXJW062 and to attribute all toxicity to the isomer DPX-KN128 (indoxacarb) a correction factor of 2 was applied to the NOAEL, resulting in a NOAEL of 0.68 mg/kg body weight (bw) per day. This approach was agreed by the ecotoxicologists and used in the risk assessment for mammals. However, the mammalian toxicology experts concluded that none of the enantiomers should be considered more toxic than the others. Therefore, the use of the correction factor was further considered by the Pesticides Peer Review Experts' meeting 8 in June 2019. At this meeting, the experts concluded that a correction factor is not needed in line with the mammalian toxicology conclusion. Therefore, a NOAEL of 1.361 mg/kg bw per day was agreed. By using this endpoint, the outcome of the risk assessment in the EFSA Conclusion (EFSA, 2018) remains unchanged. Indeed, the updated long-term risk to mammals (see toxicity/exposure ratios (TERs) in Table 1) was still high for small herbivorous mammals 'vole' for the representative use on maize. Therefore, a refined long-term risk assessment was still triggered.

Table 1: Long-term toxicity/exposure ratios (TERs) for mammals for the representative use on maize at 37.5 g a.s./ha (2 applications)

| Growth stage | Indicator or focal species | DDD (mg/kg bw per day) | TER | Trigger |
|-----------------------|------------------------------------|------------------------|-------------|---------|
| Screening step | | | | |
| All | Small herbivorous mammals | 1.87 | 0.64 | 5 |
| Tier 1 | | | | |
| BBCH \geq 20 | Small insectivorous mammal 'shrew' | 0.05 | 27.8 | 5 |
| BBCH 30–39 | Small herbivorous mammal 'vole' | 0.94 | 1.4 | 5 |
| BBCH \geq 40 | Small herbivorous mammal 'vole' | 0.47 | 3.0 | 5 |
| BBCH 30–39 | Small omnivorous mammal 'mouse' | 0.10 | 13.4 | 5 |
| BBCH \geq 40 | Small omnivorous mammal 'mouse' | 0.05 | 27.8 | 5 |

a.s.: active substance; BBCH: growth stages of mono- and dicotyledonous plants; DDD: daily dietary dose; bw: body weight. Bold indicates TER values below the trigger.

2.1.2. Refinement of the risk to herbivorous mammals

In order to refine the long-term risk assessment for mammals, new information provided by the applicant and reported in the updated RAR (France, 2019) along with the available refinement options in the EFSA Conclusion (EFSA, 2018) were considered in the Pesticides Peer Review Experts' meeting 8 in June 2019.

The Residue per Unit Dose (RUD) refinement was proposed for small herbivorous mammals 'vole' using data on leaves for maize. This refinement was not available in EFSA (2018) and was discussed during the Pesticides Peer Review Experts' meeting 8 held in June 2019. The experts highlighted several concerns in particular as follows: nine trials were not considered enough to replace the standard RUD values available in EFSA (2009) guidance which are based on a larger residue data set; the substance specificity of the trials cannot be used to support the uses of this refined RUD. Therefore, it was concluded that the refinement of the RUD values could not be used in the risk assessment for long-term small herbivorous mammals.

Furthermore, the DT₅₀ in lettuce, available in the EFSA Conclusion (EFSA, 2018), was considered by the experts not suitable to refine the long-term risk for the use in maize because information to support the extrapolation of data from lettuce to maize was not provided.

The fraction of food type in diet (PD) values presented in the EFSA Conclusion (EFSA, 2018) for refining the diet of the 'vole' were not considered acceptable as the data were taken from a real species which had not been established as a relevant focal species for the intended use on maize.

Overall, no acceptable refinements were available for long-term small herbivorous mammals even considering the new information provided, and therefore a high long-term risk was concluded for indoxacarb for the representative uses in maize.

2.1.3. Risk to herbivorous mammals for a single application in maize (BBCH 34–77)

Following the request from the European Commission, an assessment of the long-term risk to herbivorous mammals for a single application of 37.5 g a.s./ha in maize based on the data available during the peer review and separated for growth stages before and after BBCH growth stage 40 was performed. The results of this risk assessment (see Table 2) showed that the long-term risk for small herbivorous mammals remains high even considering only part of the representative use in maize evaluated in the EFSA Conclusion (EFSA, 2018), i.e. only a single application in maize against two applications reported in the GAP table (see Appendix A in EFSA, 2018).

Table 2: Long-term toxicity/exposure ratios (TERs) for mammals for the representative use on maize at 37.5 g a.s./ha (1 application) for growth stages before and after BBCH 40

| Growth stage | Indicator or focal species | DDD (mg/kg bw per day) | TER | Trigger |
|--------------|---------------------------------|------------------------|------------|---------|
| BBCH 30–39 | Small herbivorous mammal 'vole' | 0.72 | 1.9 | 5 |
| BBCH ≥ 40 | Small herbivorous mammal 'vole' | 0.36 | 3.8 | 5 |

a.s.: active substance; BBCH: growth stages of mono- and dicotyledonous plants; DDD: daily dietary dose; bw: body weight. Bold indicates TER values below the trigger.

2.1.4. Risk to earthworm-eating mammals

The risk assessment for earthworm-eating mammals was updated in accordance with the new agreed long-term endpoint for mammals of 1.361 mg/kg bw per day. The risk resulted high for multiple applications at BBCH 34–77 (see Table 3).

Following the request from the European Commission, calculations were performed also for single and multiple applications for BBCH codes above and below 40; these uses deviate from the representative uses considered under the peer review of indoxacarb reported in the EFSA Conclusion (EFSA, 2018). The risk for earthworm-eating mammals resulted low for a single application at BBCH growth stage above and below 40, and for multiple applications at BBCH above 40 (see Table 3).

The RMS highlighted that the applicant had indicated that an earthworm bioaccumulation study was performed, but this study was not available.

Table 3: Long-term toxicity/exposure ratios (TERs) for earthworm-eating mammals for the representative use on maize

| Growth stage | Indicator or focal species | DDD (mg/kg bw per day) | TER | Trigger |
|---------------------------|----------------------------|------------------------|-------------|---------|
| 2 applications BBCH 34–77 | Earthworm-eating mammals | 0.28 | 4.95 | 5 |
| 2 applications BBCH 40–77 | Earthworm-eating mammals | 0.18 | 7.66 | 5 |
| 1 application BBCH 34–39 | Earthworm-eating mammals | 0.25 | 5.34 | 5 |
| 1 application BBCH 40–77 | Earthworm-eating mammals | 0.1 | 13.5 | 5 |

BBCH: growth stages of mono- and dicotyledonous plants; DDD: daily dietary dose; bw: body weight. Bold indicates TER values below the trigger.

2.2. Risk assessment for bees including the possibility of risk mitigation measures

Following the EFSA guidance (2013), high risk to adult (acute contact, acute oral and chronic) honeybees and bumble bees (acute contact and oral) was concluded from exposure to indoxacarb at first tier for the treated crops and weeds scenarios for the representative uses on maize (EFSA, 2018). Furthermore, high risk was concluded for brood development.

For the treated crops, mitigation measures, such as not to apply during flowering, were proposed to address the risk. However, based on the studies in the dossier, no robust data were available to quantify these measures nor the period of time before flowering which would be needed to ensure a low risk to bees. Therefore, for the treated crops high risk is concluded for applications made up to BBCH growth stage 70 and low risk only for applications made after BBCH 70 (i.e. post-flowering period).

Regarding risk via residues in flowering weeds, avoiding application when weeds are flowering cannot cover the risk if application occurs before flowering. This mitigation measure was not considered acceptable as no data were available to demonstrate a safe pre-flowering application interval, and therefore a high risk was concluded to bees for the weeds scenario for the representative uses on maize.

3. Conclusions

The tier 1 long-term risk is high for small herbivorous mammals 'vole' for indoxacarb for the representative uses on maize when applying the NOAEL of 1.361 mg/kg bw per day in line with the mammalian toxicology peer review. No acceptable refinements are available for long-term small herbivorous mammals even considering the new information provided, and therefore, a high long-term risk for small herbivorous mammals is concluded for the representative uses on maize. Therefore, the critical area of concern identified in the EFSA Conclusion (EFSA, 2018) is retained.

The long-term risk remains high for small herbivorous mammals also considering only part of the representative use in maize evaluated in the EFSA Conclusion (EFSA, 2018), i.e. single application in maize for separated growth stages before or after BBCH 40.

A high risk for earthworm-eating mammals is concluded from secondary poisoning for the representative uses of indoxacarb on maize considering multiple applications at BBCH 34–77, and therefore the critical area of concern identified in the EFSA Conclusion (EFSA, 2018) is retained. The updated risk assessment for earthworm-eating mammals results to be low for a single application at BBCH growth stage above and below 40, and for multiple applications at BBCH above 40. Therefore, it can be concluded that for the representative use in maize evaluated in the EFSA Conclusion (EFSA, 2018), under particular conditions such as a single application or multiple applications at BBCH above 40, a low risk to earthworm-eating mammals can be identified.

For adult (acute contact, acute oral and chronic) honeybees and bumble bees (acute contact and oral), high risk is concluded from exposure to indoxacarb for the treated crops for applications made up to BBCH 70 and low risk after BBCH 70 (i.e. post-flowering period), and a high risk is concluded for the weeds scenarios for the representative uses on maize. The mitigation measures proposed for both scenarios are not considered acceptable, and therefore the critical area of concern identified in the EFSA Conclusion (EFSA, 2018) is maintained.

References

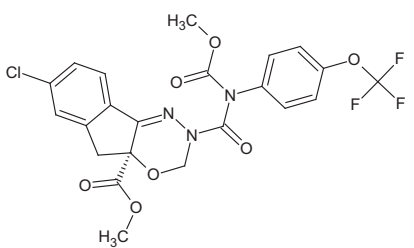
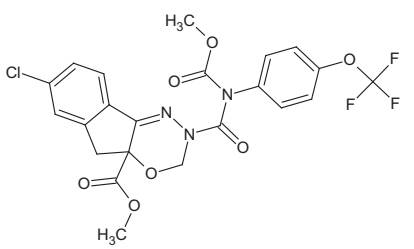
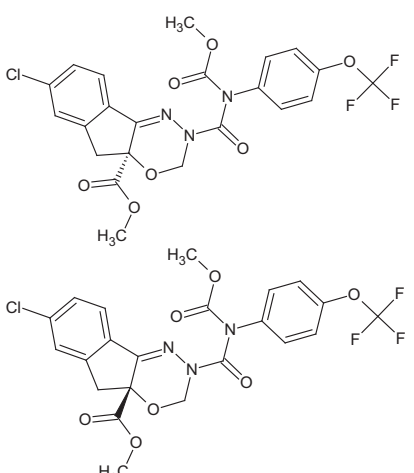
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Glossary and abbreviations

| | |
|------------------|---|
| a.s. | active substance |
| BBCH | growth stages of mono- and dicotyledonous plants |
| co-RMS | co-rapporteur Member State |
| DDD | daily dietary dose |
| EC | emulsifiable concentrate |
| DT ₅₀ | period required for 50% dissipation (define method of estimation) |
| GAP | Good Agricultural Practice |

| | |
|----------|---|
| InChiKey | International Chemical Identifier Key |
| IUPAC | International Union of Pure and Applied Chemistry |
| NOAEL | no observed adverse effect level |
| PD | proportion of different food types |
| RAR | Renewal Assessment Report |
| RMS | rappporteur Member State |
| RUD | residue per unit dose |
| SMILES | simplified molecular-input line-entry system |
| TER | toxicity exposure ratio |

Appendix A – Used compound codes

| Code/trivial name | IUPAC name/SMILES notation/ InChiKey ^(a) | Structural formula ^(b) |
|---|--|---|
| indoxacarb DPX-KN128 | methyl (<i>S</i>)-7-chloro-2,3,4a,5-tetrahydro-2- [methoxycarbonyl(4-trifluoromethoxyphenyl) carbamoyl]indeno[1,2- <i>e</i>][1,3,4]oxadiazine-4a- carboxylate <chem>FC(F)(F)Oc1ccc(cc1)N(C(=O)OC)C(=O)N1N=C2c3ccc(Cl)cc3C[C@@]2(OC1)C(=O)OC</chem> VBCVPMMZEGZULK-NRFANRHFS-A-N |  |
| DPX-JW062 racemate (50:50 of DPX-KN128:IN-KN127) | methyl (<i>RS</i>)-7-chloro-2,3,4a,5-tetrahydro-2- [methoxycarbonyl(4-trifluoromethoxyphenyl) carbamoyl]indeno[1,2- <i>e</i>][1,3,4]oxadiazine-4a- carboxylate <chem>FC(F)(F)Oc1ccc(cc1)N(C(=O)OC)C(=O)N1N=C2c3ccc(Cl)cc3CC2(OC1)C(=O)OC</chem> VBCVPMMZEGZULK-UHFFFAOYSA-N |  |
| DPX-MP062 75% DPX-KN128 and 25% IN-KN127 (insecticidally inactive enantiomer) | methyl (<i>S</i>)-7-chloro-2,3,4a,5-tetrahydro-2- [methoxycarbonyl(4-trifluoromethoxyphenyl) carbamoyl]indeno[1,2- <i>e</i>][1,3,4]oxadiazine-4a- carboxylate VBCVPMMZEGZULK-NRFANRHFS-A-N methyl (<i>R</i>)-7-chloro-2,3,4a,5-tetrahydro-2- [methoxycarbonyl(4-trifluoromethoxyphenyl) carbamoyl]indeno[1,2- <i>e</i>][1,3,4]oxadiazine-4a- carboxylate <chem>FC(F)(F)Oc1ccc(cc1)N(C(=O)OC)C(=O)N1N=C2c3ccc(Cl)cc3C[C@]2(OC1)C(=O)OC</chem> VBCVPMMZEGZULK-OAQYLSRUSA-N |  |

IUPAC: International Union of Pure and Applied Chemistry; SMILES: simplified molecular-input line-entry system;
InChiKey: International Chemical Identifier Key.

(a): ACD/Name 2018.2.2 ACD/Labs 2018 Release (File version N50E41, Build 103230, 21 July 2018).

(b): ACD/ChemSketch 2018.2.2 ACD/Labs 2018 Release (File version C60H41, Build 106041, 7 December 2018).