CONCLUSION ON PESTICIDES PEER REVIEW

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Peer review of the pesticide risk assessment of the active substance indoxacarb

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Abstract

The conclusions of EFSA following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State, France, and co-rapporteur Member State, Spain, for the pesticide active substance indoxacarb are reported. The context of the peer review was that required by Commission Implementing Regulation (EU) No 844/2012. The conclusions were reached on the basis of the evaluation of the representative uses of indoxacarb as an insecticide on maize, sweet corn and lettuce. The reliable endpoints, appropriate for use in regulatory risk assessment, are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are identified.

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

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Amendment: Following request from the European Commission, the ecotoxicology section has been updated to clarify the risk assessment for bees according to the pertinent European Commission Guidance (SANCO/10329/2002-rev.2 final, 17 October 2002). As a consequence, sections 5, 9.2 and 9.3 have been updated to reflect the outcome of the risk assessment to bees accordingly. To avoid confusion, the older version has been removed from the EFSA Journal, but is available on request, as is a version showing all the changes made.

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Summary

Commission Implementing Regulation (EU) No 844/2012 (hereinafter referred to as 'the Regulation') lays down the procedure for the renewal of the approval of active substances submitted under Article 14 of Regulation (EC) No 1107/2009. The list of those substances is established in Commission Implementing Regulation (EU) No 686/2012. Indoxacarb is one of the active substances listed in Regulation (EU) No 686/2012.

In accordance with Article 1 of the Regulation, the rapporteur Member State (RMS), France, and co-rapporteur Member State (co-RMS), Spain, received an application from DuPont de Nemours (Deutschland) GmbH for the renewal of approval of the active substance indoxacarb. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (Spain), the European Commission and the European Food Safety Authority (EFSA) about the admissibility.

The RMS provided its initial evaluation of the dossier on indoxacarb in the renewal assessment report (RAR), which was received by EFSA on 28 November 2016. In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, DuPont de Nemours (Deutschland) GmbH, for comments on 16 January 2017. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 22 March 2017.

Following consideration of the comments received on the RAR, it was concluded that additional information should be requested from the applicant, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology and residues.

In accordance with Article 13(1) of the Regulation, EFSA should adopt a conclusion on whether indoxacarb can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 of the European Parliament and of the Council.

The conclusions laid down in this report were reached on the basis of the evaluation of the representative uses of indoxacarb as an insecticide on maize, sweet corn and lettuce, as proposed by the applicant. Full details of the representative uses can be found in Appendix A of this report.

The uses of indoxacarb according to the representative uses proposed at the European Union (EU) level result in a sufficient insecticidal efficacy against the target organisms.

A data gap was identified for a search of the scientific peer-reviewed open literature, in particular as regards relevant metabolites.

In the area of identity, physical/chemical properties and analytical methods, data gaps were identified for verification of the efficiency of the extraction procedure used in the analytical methods for the determination of residues in dry commodity and for an independent laboratory validation (ILV) of the monitoring method for determination of residues in fat matrix.

Concerning the mammalian toxicology section, a data gap is identified for a comparative *in vitro* metabolism study, leading to an issue that could not be finalised. For operators, the exposure estimates are below the acceptable operator exposure level (AOEL) with the use of personal protective equipment. For workers re-entering maize and sweet corn fields, the exposure estimates are below the AOEL with the use of personal protective equipment. For workers re-entering lettuce fields after four applications, exposure estimates are above the AOEL even with the use of gloves.

In the residue section, the consumer dietary risk assessment cannot be finalised considering the outstanding data for confined rotational crops metabolism studies addressing the potential uptake and fate of indoxacarb, IN-MK643, IN-ML438, IN-JT333 and IN-JU873 in leafy crops, small grain crops and root crops; the data gap for additional northern Europe (NEU) and southern Europe (SEU) Good Agricultural Practice (GAP)-compliant residue trials on maize grain and forage (with a possible extrapolation from immature maize grain to sweet corn) and on lettuce with the representative 'EC' (emulsifiable concentrate) formulation and the data gap for confirmation that the structure of IN-VRN79 corresponds to metabolite 'F' in the poultry metabolism study. A chronic intake concern was not identified using the maximum residue level (MRL) proposals for the representative uses and for animal matrices (theoretical maximum daily intake (TMDI): 17.4% of the acceptable daily intake (ADI), Spanish adult). An acute intake concern was however identified for lettuce (international estimated short-term intake (IESTI): 457.4% of the acute reference dose (ARfD), German child). Considering the highest residue levels related to the uses evaluated under the Article 12 MRL review, a significant exceedance of the ARfD was identified for several food commodities. Therefore, the MRLs listed in the EU legislation for these food commodities need to be reconsidered.

Finally, the data requirement for the determination of residues of indoxacarb and/or its degradation products in pollen and bee products for human consumption resulting from residues taken up by honeybees from maize at blossom could not be addressed.

An MRL application has been provided for the submission of the confirmatory data to address the data gaps identified following the review of the MRLs according to Article 12 of Regulation (EC) No 396/2005. EFSA concluded that the data gaps identified for eight residue trials compliant with the import tolerance on broccoli and cauliflower, and four residue trials compliant with the southern outdoor GAP on lamb's lettuce, rocket, rucola and leaves and sprouts of brassica have not been addressed.

With respect to the fate and behaviour in the environment, a number of data gaps have been identified to finalise the exposure assessment: soil degradation and adsorption studies and exposure assessment for metabolite IN-U8E24; to further investigate identification and characterisation of the unidentified polar fraction and the identity of metabolite IN-ML437-OH in the study of Singles (2002) in France, 2017; exposure assessment for the aquatic environment for aqueous photolysis metabolites (IN-MF014, IN-C0639, IN-MA573 and IN-MH304); information to address degradation of indoxacarb in acidic water sediment systems and information to address the effect of water treatment processes on the nature of the residues that might be present in surface water and groundwater, when surface water or groundwater is abstracted for drinking water.

In the area of ecotoxicology, for indoxacarb, a high long-term risk was concluded for small herbivorous mammals for the representative uses on maize and for small insectivorous, small herbivorous and small omnivorous mammals for the representative uses on lettuce, as well as a high risk was concluded for earthworm-eating mammals from secondary poisoning, leading to a critical area of concern. In addition, data gaps were identified for the risk assessment for birds and wild mammals from secondary poisoning for the relevant metabolites (assessment not finalised), for the risk for birds from consumption of contaminated water and for the risk assessment for bees. A high acute risk was concluded for honeybees for all representative uses, leading to a critical area of concern. Based on a screening assessment, a low risk could not be concluded for sediment-dwelling organisms for several metabolites (assessment not finalised). A data gap was also identified to assess the risk for the aqueous photolysis metabolites IN-MF014, IN-C0639, IN-MA573 and IN-MH304 (assessment not finalised).

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Background

Commission Implementing Regulation (EU) No 844/2012[1] (hereinafter referred to as 'the Regulation') lays down the provisions for the procedure of the renewal of the approval of active substances, submitted under Article 14 of Regulation (EC) No 1107/2009.[2] This regulates for the European Food Safety Authority (EFSA) the procedure for organising the consultation of Member States, the applicant(s) and the public on the initial evaluation provided by the rapporteur Member State (RMS) and/or co-rapporteur Member State (co-RMS) in the renewal assessment report (RAR), and the organisation of an expert consultation where appropriate.

In accordance with Article 13 of the Regulation, unless formally informed by the European Commission that a conclusion is not necessary, EFSA is required to adopt a conclusion on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 within 5 months from the end of the period provided for the submission of written comments, subject to an extension of an additional 3 months where additional information is required to be submitted by the applicant(s) in accordance with Article 13(3).

In accordance with Article 1 of the Regulation, the RMS, France, and co-RMS, Spain, received an application from DuPont de Nemours (Deutschland) GmbH for the renewal of approval of the active substance indoxacarb. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (Spain), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on indoxacarb in the RAR, which was received by EFSA on 28 November 2016 (France, 2016).

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, DuPont de Nemours (Deutschland) GmbH, for consultation and comments on 16 January 2017. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 22 March 2017. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicant was invited to respond to the comments in column 3 of the reporting table. The comments and the applicant's response were evaluated by the RMS in column 3.

The need for expert consultation and the necessity for additional information to be submitted by the applicant in accordance with Article 13(3) of the Regulation were considered in a telephone conference between EFSA, the RMS and co-RMS on 5 May 2017. On the basis of the comments received, the applicant's response to the comments and the RMS's evaluation thereof, it was concluded that additional information should be requested from the applicant, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology and residues.

The outcome of the telephone conference, together with EFSA's further consideration of the comments, is reflected in the conclusions set out in column 4 of the reporting table. All points that were identified as unresolved at the end of the comment evaluation phase and which required further consideration, including those issues to be considered in an expert consultation, were compiled by EFSA in the format of an evaluation table.

The conclusions arising from the consideration by EFSA, and as appropriate by the RMS, of the points identified in the evaluation table, together with the outcome of the expert consultation and the written consultation on the assessment of additional information, where these took place, were reported in the final column of the evaluation table.

A final consultation on the conclusions arising from the peer review of the risk assessment took place with Member States via a written procedure in November 2017.

This conclusion report summarises the outcome of the peer review of the risk assessment of the active substance and the representative formulation evaluated on the basis of the representative uses of indoxacarb as an insecticide on maize, sweet corn and lettuce as proposed by the applicant. A list of the relevant endpoints for the active substance and the formulation is provided in Appendix A.

[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] Regulation (EC) No 1107/2009 of 21 October 2009 of the European Parliament and of the Council 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.

In addition, a key supporting document to this conclusion is the peer review report (EFSA, 2017), which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the initial commenting phase to the conclusion. The peer review report comprises the following documents, in which all views expressed during the course of the peer review, including minority views, where applicable, can be found:

- the comments received on the RAR;
- the reporting table (8 May 2017);
- the evaluation table (11 December 2017);
- the reports of the scientific consultation with Member State experts (where relevant);
- the comments received on the assessment of the additional information (where relevant);
- the comments received on the draft EFSA conclusion.

Given the importance of the RAR, including its revisions (France, 2017), and the peer review report, both documents are considered as background documents to this conclusion and thus are made publicly available.

It is recommended that this conclusion report and its background documents would not be accepted to support any registration outside the European Union (EU), for which the applicant has not demonstrated that it has regulatory access to the information on which this conclusion report is based.

The active substance and the formulated product

Indoxacarb is the ISO common name for methyl (*S*)-*N*-[7-chloro-2,3,4a,5-tetrahydro-4a-(methoxycarbonyl)indeno[1,2-*e*][1,3,4]oxadiazin-2-ylcarbonyl]-4′-(trifluoromethoxy)carbanilate or methyl (*S*)-7-chloro-2,3,4a,5-tetrahydro-2-[methoxycarbonyl(4-trifluoromethoxyphenyl)carbamoyl]indeno[1,2-*e*][1,3,4]oxadiazine-4a-carboxylate (IUPAC).

The representative formulated product for the evaluation was 'Indoxacarb 150 g/L EC', an emulsifiable concentrate (EC) containing 150 g/L indoxacarb.

The representative uses evaluated were spray applications, by tractor-mounted hydraulic field sprayers with ground-directed booms, for the control of lepidopteran insect pests in lettuce, maize (grain and forage) and sweet corn and for the control of the coleopteran insect pest *Diabrotica virgifera* in maize and sweet corn. Full details of the Good Agricultural Practices (GAPs) can be found in the list of endpoints in Appendix A.

Data were submitted to conclude that the uses of indoxacarb according to the representative uses proposed at the EU level result in a sufficient insecticidal efficacy against the target organisms, following the guidance document SANCO/2012/11251-rev. 4 (European Commission, 2014).

A data gap has been identified for a search of the scientific peer-reviewed open literature, in particular as regards relevant metabolites in accordance with EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011a).

Conclusions of the evaluation

1. Identity, physical/chemical/technical properties and methods of analysis

The following guidance documents were followed in the production of this conclusion: SANCO/3029/99-rev. 4 (European Commission, 2000a), SANCO/3030/99-rev. 4 (European Commission, 2000b) and SANCO/825/00-rev. 8.1 (European Commission, 2010).

The reference specification for first approval was updated since the manufacturing process has been changed in order to produce specifically the (*S*)-enantiomer; therefore, the ratio of enantiomers is different to the ratio defined during the first inclusion. The proposed specification is based on batch data from industrial scale production. The proposed minimum purity of the technical material is 930 g/kg. Toluene, bis(diethylamino)diphenylmethane (IN-06439), bis(4-diethylaminophenyl)methanol (IN-R1T94), bis(diethylamino)benzophenone (IN-C0800) and tris(*p*-(diethylamino)phenyl)methylium chloride (IN-J1063) are considered relevant impurities with a maximum content of 14 g/kg, 0.0025, 0.0025, 0.0025 and 0.0018 g/kg, respectively. It should be noted that apart from toluene, the other maximum content values are based on the limit of the quantification (LOQ). The manufactured technical material meets the requirements of the existing FAO specification (612/TC, June 2009) in terms of minimum purity; relevant impurities are not mentioned in the FAO specification.

The batches used in the (eco)toxicological assessment support the proposed new reference specification.

The assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the identity, physical, chemical and technical properties of indoxacarb or the representative formulation. The main data regarding the identity of indoxacarb and its physical and chemical properties are given in Appendix A.

Adequate methods are available for the generation of pre-approval data required for the risk assessment. Methods of analysis are available for the determination of the active substance and the relevant impurities in the technical material and in the representative formulation.

Indoxacarb residues can be monitored in food and feed of plant origin by multiresidue DFG S19 method using liquid chromatography with tandem mass spectrometry (LC–MS/MS), with a LOQ of 0.01 mg/kg in each commodity group. It should be noted that the efficiency of the extraction procedure used was not verified for dry commodity (data gap). The LC–MS/MS method exists for determination of indoxacarb residues in honey with a LOQ 0.01 mg/kg. Residues of indoxacarb and metabolite IN-JT333 in milk, eggs, fat, muscles and liver can be determined by DFG S19 LC–MS/MS with a LOQ of 0.01 mg/kg in each animal matrices. Residues of indoxacarb and metabolite IN-JT333 in fat matrix can also be monitored by LC–MS/MS with a LOQ of 0.002 mg/kg. However, it should be

noted that a data gap was identified for an independent laboratory validation (ILV) of the methods for fat matrix.

Indoxacarb residues in environmental matrices can be monitored by LC–MS/MS with LOQs of 0.001 mg/kg in soil, 0.05 μg/L in water and 0.10 μg/m^3 in air.

LC–MS/MS can be used for monitoring indoxacarb residues in body fluids with a LOQ of 0.002 mg/L. Indoxacarb residues in body tissues can be determined by using the monitoring methods for residues in food of animal origin.

2. Mammalian toxicity

The toxicological profile of the active substance indoxacarb and its metabolites was discussed at the Pesticides Peer Review Experts' Meeting 162 (September 2017) and assessed based on the following guidance documents: SANCO/221/2000-rev. 10-final (European Commission, 2003), SANCO/10597/2003-rev. 10.1 (European Commission, 2012) and Guidance on dermal absorption (EFSA PPR Panel, 2012).

To assess the toxicological profile of the **active substance**, the applicant submitted a complete set of valid toxicity studies. The batches used in the toxicity studies were concluded as being representative of the new technical specification for the active substance. Five relevant impurities have been identified, toluene (max. 14 g/kg), IN-J1063 (max. 0.0018 g/kg), IN-C0800, IN-R1T94 and IN-06439 (max. 0.0025 g/kg).

The new technical specification defines indoxacarb (DPX-KN128) as the almost pure active *S*-isomer. However, the technical specification for the first inclusion was a mixture of isomers proposed based on studies performed with two mixtures: the racemic (DPX-JW062) and the ratio 75*S*:25*R* (DPX-MP062). For the purpose of the renewal, the RAR includes toxicity studies performed with the different isomer ratios of indoxacarb: indoxacarb (DPX-KN128), indoxacarb 75*S*:25*R* (DPX-MP062) or with the racemic mixture (DPX-JW062). The experts agreed that none of the enantiomers should be considered more toxic than the others, meaning that DPX-KN128 containing the highest proportion of active enantiomer is not considered more toxic. Therefore, the studies conducted with the less active enantiomer than indoxacarb (DPX-KN128) are also considered relevant for the purpose of the renewal.

In the toxicokinetic studies, oral absorption is estimated to be 60%. Indoxacarb is found mainly in fat and blood with a sex specificity (higher tissue levels in females) and with a potential of accumulation in fat and red blood cells. It is extensively metabolised and slowly excreted via urine and faeces. A comparative *in vitro* metabolism study has not been submitted, leading to a data gap and an issue that could not be finalised.

In most studies in the rat, females appear to be more sensitive than males. Species differences are also observed with rats being more sensitive than mice and dogs to the toxicological effects.

In the acute toxicity studies, indoxacarb is toxic by oral route, harmful by inhalation and is of low toxicity dermally.[3] It is not a skin or eye irritant. However, indoxacarb is a skin sensitiser in Magnusson and Kligman tests and classified as Skin Sens 1B[3]. Based on a phototoxicity study, indoxacarb is not phototoxic and a photomutagenicity study is not required as its molar extinction/absorption coefficient is less than 1,000 L $\times$ mol^{-1} $\times$ cm^{-1}.

In short-term toxicity studies, the main toxic effects are observed on the haematological parameters and related organs (spleen and/or bone marrow). In two 90-day rat studies, no observed adverse effect levels (NOAELs) of 0.68 and 0.99 mg/kg body weight (bw) per day are identified, whereas in a third study, a lowest observable adverse effect level (LOAEL) of 0.76 mg/kg bw per day is agreed. In a 90-day mouse study, the NOAEL has been determined to be 5.5 mg/kg bw per day. For the dog studies (90-day and 1-year), a LOAEL of 1 mg/kg bw per day has been identified. By dermal route, in the 28-day study in rats, a LOAEL of 50 mg/kg bw per day is established.

Indoxacarb is unlikely to be genotoxic based on *in vitro* tests: Ames test, mammalian cell gene mutation, chromosome aberration and unscheduled DNA synthesis; and based on negative results in *in vivo* micronucleus test in mice.

In the 2-year rat study, the NOAEL is 1.04 mg/kg bw per day based on haemolytic effects and related histopathological findings in the liver and spleen. In the 18-month mouse study, the NOAEL is 2.63 mg/kg bw per day based on decreased body weight gain and food consumption and clinical signs

[3] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, 1–1355.

of neurotoxicity. Indoxacarb was concluded as unlikely to be carcinogenic by the experts, considering the negative results with the racemic mixture, the lack of genotoxic potential of the other isomeric ratios DPX-MP062 and DPX-KN128 and the fact that the different ratios show similar effects at a similar range of dose levels in short-term studies.

In the multigeneration rat study, the offspring's NOAEL is 1.2 mg/kg bw per day based on decreased body weight in F1 pups during lactation. The parental NOAEL is 1.2 mg/kg bw per day based on decreased body weight gain and food consumption and increased spleen weight and the reproductive NOAEL is 6.1 mg/kg bw per day (high dose tested). In the developmental rat studies, the lowest maternal NOAEL is 0.5 mg/kg bw per day based on decreased body weight gain and the lowest developmental NOAEL is 3.5 mg/kg bw per day (high dose tested). In the developmental study in rabbit, the maternal NOAEL is 500 mg/kg bw per day based on decreased body weight gain and food consumption, and the developmental NOAEL is 500 mg/kg bw per day based on decreased mean foetal weights and retarded sternebral ossification. Indoxacarb is concluded as unlikely to be teratogenic.

In acute and repeated rat neurotoxicity studies, the NOAELs for neurotoxicity are 50 mg/kg bw based on decreased motor activity in females and 6.09 mg/kg bw per day (highest dose tested), respectively. In a developmental rat neurotoxicity study, the maternal NOAEL is determined at 1 mg/kg bw per day based on effects on body weight gain and the offspring NOAEL is 1.5 mg/kg bw per day based on increased number of stillborn pups, increased pup mortality and decreased pup weight.

Based on the immunotoxicity mouse study, indoxacarb does not show any effect on the humoral immune response.

The harmonised classification[3] of indoxacarb as STOT RE1 H372 (causes damage to organs through prolonged or repeated exposure) is based on effects reported on blood, heart and nervous system in repeat dose toxicity studies. Indoxacarb is not classified or proposed to be classified as toxic for reproduction category 2 or carcinogenic category 2, in accordance with the provisions of Regulation (EC) No 1272/2008, and therefore, the conditions of the interim provisions of Annex II, point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine disrupting properties are not met. With regard to the scientific risk assessment, considering that there are no histopathological effects on endocrine-related tissues and any effects on reproduction or fertility together with the results from US EPA ToxCast and Endocrine Disruptor Screening Program, the experts agreed that indoxacarb is unlikely to have endocrine disrupting properties.

The acceptable daily intake (ADI) for indoxacarb is 0.005 mg/kg bw per day based on the decreased maternal body weight gain in the developmental rat study, and applying an uncertainty factor (UF) of 100 (0.006 mg/kg bw per day based on two-year rat study (overall NOAEL 0.6 mg/kg bw per day) during the first peer review (European Commission, 2005)). The acceptable operator exposure level (AOEL) is 0.003 mg/kg bw per day based on the developmental rat study, applying an UF of 100 and a correction for a limited oral absorption (60%) (0.004 mg/kg bw per day based on 90-day rat study (overall NOAEL 0.6 mg/kg bw per day and correction for 60% oral absorption) during the first peer review). The setting of an acute reference dose (ARfD) is proposed at 0.005 mg/kg bw based on the decreased maternal body weight gain in the developmental rat study applying an UF of 100 (0.125 mg/kg bw based on acute rat neurotoxicity study during the first peer review). The acute AOEL (AAOEL) is set at 0.003 mg/kg bw based on the developmental rat study, applying an UF of 100 and a correction for a limited oral absorption (60%).

Based on an *in vivo* rat study and *in vitro* rat/human skin study testing, the representative formulation, the dermal absorption values for indoxacarb are 1% for the concentrate and 18% for the dilution with the triple pack approach used as refinement. Exposure estimates were provided for the representative uses on maize, sweet corn and lettuce. For the operators, the predicted exposure is below the AOEL with the use of personal protective equipment (PPE) (German model). For the residents and bystanders, both predictions with EUROPOEM II and the German model gave results below the AOEL (at 1, 7 and 10 m). For the workers re-entering maize and sweet corn fields after two applications, exposure estimates with EUROPOEM II are below the AOEL with the use of PPE, whereas for workers re-entering lettuce fields after four applications, exposure estimates are above the AOEL even with the use of gloves.

It is noted that, for information purposes, exposure estimates with the EFSA calculator (EFSA, 2014) were also provided in the final RAR (France, 2017).

Concerning **the metabolites**, the metabolite IN-JT333 is unlikely to be genotoxic, but the relative toxicity compared to the parent compound is unknown (90-day rat study ongoing). However, no data gap has been identified as considering the representative uses residues above 0.01 mg/kg are not

expected in poultry matrices (see Section 3). The metabolites IN-KT413, IN-MP819, IN-TMG00, 5-OH-IN-JT333, 5-OH-DPXJW062 and IN-KG433 are considered unlikely to be genotoxic. The metabolite IN-P0036 is considered as covered by studies performed with the parent compound. For the metabolites IN-MF014, IN-MN470, IN-MK638 and IN-MT713, their toxicity profile (including genotoxicity) cannot be concluded; however, no data gap has been identified for the representative uses (see Section 3).

3. Residues

The assessment in the residue section is based on the OECD guidance document on overview of residue chemistry studies (OECD, 2009), the OECD publication on maximum residue level (MRL) calculations (OECD, 2011), the European Commission guideline document on MRL setting (European Commission, 2011) and the Joint Meeting on Pesticide Residues (JMPR) recommendations on livestock burden calculations (JMPR, 2004, 2007).

Indoxacarb was discussed at the Pesticides Peer Review Experts' Meeting 164 in September 2017.

Metabolism of indoxacarb in primary crops was investigated upon foliar application on pulses and oilseeds (cotton), fruit (grapes, tomatoes) and on leafy (lettuce) crop groups using the racemic mixture DPX-JW062 ^{14}C-labelled on the indanone moiety and the trifluoromethoxyphenyl ring, respectively. In all crops and for both labellings, indoxacarb (racemic mixture) was the main compound of the total radioactive residues (TRR) accounting for up to 84% TRR in mature cotton leaves, 95% TRR in grapes, 99% TRR in lettuce and up to 87% and 97% TRR in tomato fruit and leaves, respectively. The TRRs in mature cotton seeds were too low (< 0.01 mg/kg) to perform further metabolites' identification. In mature cotton leaves and tomato fruits and leaves, the *S/R* isomeric ratio remained unchanged (1:1) indicating no preferential metabolism of either enantiomer in those crops. It is therefore unlikely that any further metabolism study conducted with the *S*-isomer only (indoxacarb) will lead to a different metabolic pattern. Considering also that the *R*- and *S*- isomers were concluded to be of similar toxicity (see Section 2), the experts of the meeting agreed that sufficient metabolism data are available to fully address the metabolism of indoxacarb in plants and a general residue definition for monitoring and risk assessment in plants can be set as indoxacarb (and its *R*-enantiomer).

A confined rotational crop metabolism study was conducted following a bare soil application (2N rate) with ^{14}C-indoxacarb labelled either on the indanone moiety or on the trifluoromethoxyphenyl ring in root crops (carrot), leafy crops (lettuce), cereals (wheat) and pulses and oilseeds (soya bean) at 36, 90 and 125 days plant-back intervals (PBIs). The study was not compliant with the current guidance recommendations in view of the lack of metabolites' identification in any edible part of the crops and significant proportions of unextracted radioactive residues (12–52% TRR). The metabolic pattern of indoxacarb in rotational crops could therefore not be elucidated. Having regard to the medium to high persistence in soil of indoxacarb (DT_{50} = 65.3–321 days) and of its metabolites: IN-MK643 (DT_{50} = 123.3–314.2 days), IN-ML438 (DT_{50} = 80.9–186.5 days), IN-JT333 (DT_{50} = 19.6–147.5 days) and IN-JU873 (DT_{50} = 24.8–103.5 days), a data gap was identified to provide confined rotational crops metabolism studies addressing the potential uptake and fate of these compounds in leafy crops, small grain crops and root crops and to enable the calculation of reliable soil/plant transfer factors for the parent indoxacarb and all relevant compounds. The need for further rotational crops field residue trials conducted at a dose of application covering the maximum predicted plateau concentration in soil of indoxacarb and all relevant compounds will have to be reconsidered accordingly.

Under standard hydrolysis conditions, indoxacarb was found to be stable under pasteurisation whilst it was degraded into IN-KT413 under baking/brewing/boiling conditions (14% of the applied radioactivity (AR)) and into the following metabolites under sterilisation: IN-KT413 (28.7% AR), IN-MP819 (10% AR), IN-MK638 (10% AR), IN-P0036 (16% AR) and IN-TMG00 (12.4% AR). Processing residue trials were submitted on tomatoes, grapes, apples, peaches and maize analysing for residues of indoxacarb and its *R*-enantiomer in processed commodities. Further processing residue trials analysing for metabolites IN-KT413, IN-MK638, IN-P0036 and IN-TMG00 in canned apples, peaches and green beans demonstrated that these compounds were never detected (< LOQ). The validity of these trials was discussed as these were not representative of the most critical conditions of sterilisation and cannot therefore be considered to rule out the occurrence of these metabolites in processed commodities. It is also noted that IN-MP819 was never analysed in any processed commodity, and finally, these processing residue trials were not supported by storage stability data to demonstrate the integrity of residues of all relevant compounds. For processed commodities, the residue definition for monitoring is proposed as indoxacarb (and its *R*-enantiomer) while for risk

assessment, the residue definition is provisionally set as indoxacarb and metabolites IN-KT413, IN-MK638, IN-P0036, IN-MP819 and IN-TMG00. All these metabolites, except IN-MK638, are unlikely to be genotoxic whilst only IN-P0036 was considered as covered by the toxicity studies of indoxacarb (see Section 2). For the representative uses and since indoxacarb residues were below the LOQ (0.01 mg/kg) in the raw agricultural commodities that may undergo a heating step (maize grain, sweet corn) and lettuce is mainly eaten raw, the consumer risk assessment with regard to processed commodities can be considered as finalised. In contrast and for any future use involving sterilisation or any heating step with similar conditions of temperature and time, processing residue trials analysing for the magnitude of all the compounds included in the provisional residue definition for risk assessment should be provided. If quantifiable residue levels of these compounds are observed, their toxicity profile should also be addressed.

Since the northern Europe (NEU) and southern Europe (SEU) residue trials submitted on maize grain and forage were conducted with a 'WG' formulation and a time interval between application that did not comply with the critical time interval (20 days), EFSA is of the opinion that sufficient NEU and SEU GAP-compliant residue trials on maize grain and forage and conducted with the DPX-KN128 150EC formulation should be provided (with a possible extrapolation from immature maize grain to sweet corn) (data gap). Meanwhile, a provisional MRL of 0.01 mg/kg (MRL is proposed at the level of LOQ.) for maize grain and sweet corn is derived. Trials compliant with the NEU and SEU GAPs on lettuce were performed with a water-dispersible granule (WG) formulation and a provisional MRL of 1.5 mg/kg was derived. Sufficient NEU and SEU bridging residue data on lettuce with the representative EC formulation should be provided to demonstrate that residues are equivalent from these formulations (data gap).The submitted residue data are supported by storage stability studies where indoxacarb residues were shown to be stable in maize grain and maize green plant (forage) for 13 months and in lettuce for 11 months.

Poultry and ruminants metabolism studies were conducted using the racemic mixture DPX-JW062 ^{14}C-labelled on the indanone moiety and the trifluoromethoxyphenyl ring, respectively. Following chiral analysis that was performed on poultry fat and ruminant milk and kidney, an enrichment of the *S*-enantiomer (indoxacarb) was observed in all matrices (ca. 2:1 in milk, kidney and 3:1 in poultry fat) and a preferential absorption of indoxacarb in those tissues is postulated.

In poultry matrices, the parent compound was found at minor proportions in all matrices except in gizzard (up to 25%), while metabolites IN-JT333, 5-OH-IN-JT333, IN-KG433 and metabolite 'F' were found to be the major compounds of the total residues (> 10% TRR) in several matrices. Metabolites IN-KB687 occurred in eggs at up to 19% TRR while metabolite IN-MK638 was identified at up to 13% TRR in eggs and 16% TRR in muscle, but their actual concentrations were low (0.01 mg/kg). The residue definition for monitoring is set as indoxacarb (and its *R*-enantiomer) and IN-JT333. A minority opinion considered that also metabolite 'F' should be included in this residue definition for monitoring. Although significant residue levels of this compound were observed in egg yolk (up to 14% TRR), muscle (13% TRR) and fat (up to 45% TRR) based on the metabolism data, metabolite 'F' was not analysed for in the poultry feeding study and whether it can be concluded as a relevant marker of the residues in all matrices cannot be ruled out. Furthermore and considering the predominance of several metabolites in poultry matrices, the agreed residue definition for risk assessment provisionally includes besides indoxacarb (and its *R*-enantiomer), metabolites IN-JT333, metabolite 'F', IN-KG433 and 5-OH-IN-JT333. Metabolite 'F' was tentatively identified as compound IN-VRN79. Since there are indications that elucidation of the structure and identification were not yet finalised at the time of the submission of the revised RAR, a data gap is identified for the applicant to declare the status of the study to verify the occurrence and confirm that the structure of IN-VRN79 corresponds to metabolite 'F' in the poultry metabolism study.

For ruminants, the parent compound (racemic mixture) was found to be the valid marker of the total residues in all matrices with levels ranging between 12% and 80% TRR. IN-MP819 compound was identified at significant proportions in milk only (up to 28% TRR) while 5-OH-DPX-JW062 accounted for up to 13% TRR in kidney and 25% TRR in muscle, but its actual concentration was low (0.01 mg eq/kg). The residue definition for monitoring was set as indoxacarb (and its *R*-enantiomer) only, while the residue definition for risk assessment is set as indoxacarb (and its *R*-enantiomer) for all matrices, except for milk where the residue definition as indoxacarb (and its *R*-enantiomer) and IN-MP819 is provisionally proposed.

Feeding studies were submitted in poultry and ruminants and were supported by acceptable storage stability data. In the poultry feeding study, the magnitude of metabolites 5-OH-IN-JT333 and metabolite 'F' was not determined while in the ruminant feeding study, metabolite IN-MP819 was not

analysed for in milk. However and considering the representative uses, residues above 0.01 mg/kg are not expected in poultry matrices and in milk and no further feeding studies addressing the magnitude of these metabolites are requested. It is, however, highlighted that for any future use leading to an increase of the dietary burden calculation, the validity of these feeding studies should be reconsidered and additional data might be needed to address the toxicity and the magnitude of all compounds included in the residue definitions for risk assessment set for poultry and ruminants matrices. For ruminants, MRLs 0.02 mg/kg for fat and 0.01 mg/kg (MRL is proposed at the level of LOQ.) for muscle, liver, kidney and milk are proposed. MRLs are not required and not proposed for poultry matrices.

A fish metabolism study was not provided and is not requested as indoxacarb residues in maize grain are below the LOQ of the method (0.01 mg/kg) and the other representative uses are not considered as feed items for fish. This assessment should be reconsidered pending upon the outcome of the requested residue trials on maize grain.

Since maize shows attractiveness to bees for pollen collection (EFSA, 2013) and treatment can take place at flowering, residues of indoxacarb and/or its degradation products in pollen and bee products cannot be excluded and further information is requested (data gap). Since lettuce is harvested before flowering, this crop is not relevant for potential exposure of bees to indoxacarb residues.

For the time being, only a provisional consumer dietary risk assessment can be conducted considering the identified data gaps. A chronic intake concern was not identified using the MRL proposals for the representative uses and for animal matrices (theoretical maximum daily intake (TMDI): 17.4% of the ADI, Spanish adult). An acute intake concern was however identified for lettuce (international estimated short-term intake (IESTI): 457.4% of the ARfD, German child).

The toxicological reference values and the residue definitions for both enforcement and risk assessment in poultry and ruminants have been changed compared to those used in the review of the existing MRLs for indoxacarb (EFSA, 2011b). Based on the proposed ADI value of 0.005 mg/kg bw per day, no chronic intake concern was identified for the consumers for all the existing uses assessed under the Article 12 MRL review (88.2% of the ADI (DE child)) when the consumer dietary intake calculation is performed including demonstrated safe EU MRLs and safe codex maximum residue limits (CXLs). In contrast and considering the ARfD value of 0.005 mg/kg bw, an exceedance of the ARfD is identified for numerous commodities (maximum IESTI: 1,964.4% of the ARfD for table grapes). Melon (1,183% of ARfD), watermelon (954% of ARfD), peaches (760% of ARfD), cucumbers (456% of ARfD), plums (421% of ARfD), apricots (396% of ARfD), courgettes (362% of ARfD), tomato (349% of ARfD), pumpkins (266% of ARfD), scaroles (961% of ARfD), lettuces (882% of ARfD), celery (854% of ARfD), apples (509% of ARfD), pears (473% of ARfD), spinach (443% of ARfD) and cauliflower (271% ARfD). The established MRLs under Article 12 of Regulation (EC) No 396/2005 should therefore be reassessed considering the finalisation of the residue definitions for risk assessment in processed commodities and in livestock matrices.

An MRL application has been provided for the submission of the confirmatory data to address the data gaps identified following the review of the MRLs according to Article 12 of Regulation (EC) No 396/2005. It is concluded that the data gaps identified for eight residue trials compliant with the import tolerance on broccoli and cauliflower and four residue trials compliant with the southern outdoor GAP on lamb's lettuce, rocket, rucola and leaves and sprouts of brassica have not been addressed.

4. Environmental fate and behaviour

The specification of the current commercial product defines indoxacarb (DPX-KN128) as the almost pure active *S*-isomer. However, the product was previously commercialised as a mixture of isomers and has been developed based on studies performed with two main mixtures DPX-JW062 (racemic) and DPX-MP062 (75*S*:25*R*). Isomeric stability was investigated and demonstrated in the laboratory degradation studies.

The rates of dissipation and degradation in the environmental matrices investigated were estimated using FOCUS (2006) kinetics guidance. In soil laboratory incubations under aerobic conditions in the dark, indoxacarb exhibited medium to high persistence, forming the following metabolites which need further assessment: IN-JT333 (max. 18.6% AR, moderate to high persistence), IN-KG433 (max. 40% AR, low to moderate persistence), IN-KT413 (max. 18.4% AR, very low to low persistence), IN-JU873 (max. 12.9% AR, moderate to high persistence), IN-ML438 (max. 9.7% AR, medium to high persistence), IN-MK638 (max. 28% AR, low to moderate), IN-KB687 (max. 6.9% AR, very low

persistence), IN-MK643 (max. 12% AR, high persistence) and IN-U8E24 for which a data gap to investigate formation and degradation in soil has been identified. Mineralisation accounted for 8.4–29% after 120 days depending on the ring system where the ^{14}C-labelled carbon was placed. The formation of unextractable residues accounted for 45–56% AR depending on the label. A data gap has been identified for soil degradation studies for metabolite IN-U8E24 (study already initiated by the applicant). Another data gap has been identified to further characterise the polar fraction and further identify metabolite IN-ML437-OH observed in the study Singles (2002) in France (2017). The applicant has already initiated a study to address this data requirement expected to be finalised by June 2019.

In the single study performed under anaerobic soil incubations, indoxacarb was low persistent. Under anaerobic conditions, the following metabolites were formed: IN-KT413 (max. 25.2% AR), IN-U8E24 (max. 40.0% AR), IN-MP819 (max. 5.9% AR), IN-KN125 (max. 10.6% AR, *S*-enantiomer of IN-JT333), IN-MS775 (max. 34.4% AR), IN-U8F52 (max. 14.7% AR) and IN-MK638 (max. 9.4% AR) of which IN-MP819, IN-MS775 and IN-U8F52 are not aerobic metabolites and may need to be further investigated if, in the future, uses for which long anaerobic conditions may prevail are to be authorised. Dissipation under field conditions was investigated in four locations in Europe. In these trials, indoxacarb dissipated with half-lives below 10 days.

Indoxacarb shows to be immobile or exhibited slight mobility in soil. IN-JT333 shows to be immobile, IN-JU873 exhibited medium to high mobility, IN-KG433 exhibited medium mobility, IN-KT413 exhibited medium mobility, IN-MK638 exhibited medium to high mobility, IN-KB687 exhibited medium mobility, IN-ML438 shows to be immobile and IN-MK643 exhibited medium mobility. For metabolite IN-U8E24, a data gap for batch adsorption studies was identified during the peer review (study already initiated by the applicant).

In laboratory incubations in dark aerobic natural sediment water systems, indoxacarb exhibited low persistence, forming the metabolites IN-JT333 (max. 25.7% AR in sediment, exhibiting medium to moderate persistence), IN-KT413 (max. 69.1% AR in water and max. 10.7% in sediment, that exhibited moderate persistence), IN-KG433 (max. 7.7% AR in sediment, persistence not reliably determined), IN-ML438 (max. 3.6% AR in sediment, that exhibited moderate to high persistence), IN-MK638 (max. 4% AR in water and max. 5% in sediment, persistence not reliably determined), IN-MP819 (max. 0.4% AR in water and max. 21.3% in sediment, persistence not reliably determined), IN-U8E24 (max. 10.5% AR in water and max. 16.0% in sediment, that exhibited moderate to high persistence), IN-UYG24 (max. 31.6% AR in water, not observed in sediment, that exhibited moderate to very high persistence) and IN-MS775 (max. 14.7% AR in sediment, persistence not reliably determined). The unextractable sediment fraction was the major sink, accounting for 23.9–66.1% AR. Mineralisation of this radiolabel accounted for 0.9–9.6% AR at the end of the study. The available water sediment studies do not cover the case of acidic range; therefore, a data gap has been identified to provide information to address degradation of indoxacarb in acidic water sediment systems. The rate of decline of indoxacarb in a laboratory aqueous photolysis experiment was comparable to degradation that occurred in the aerobic sediment water incubations. A number of metabolites were formed at levels above 10% under aqueous photolysis natural light conditions: IN-MF014 (max: 37.6% AR), IN-KB687 (max: 28.7% AR), IN-C0639 (max: 10.2% AR), IN-MA573 (max: 19.9% AR) and IN-MH304 (max: 32.3% AR). In agreement with the RMS view, these metabolites need to be considered for the aquatic environmental risk assessment. The applicant considered that on the basis of the fast adsorption observed in the water sediment studies, an aquatic risk assessment would not be needed. This was initially accepted by the RMS and during the peer review; however, the kinetics of adsorption in the laboratory water sediment experiments cannot be correlated with the one occurring in natural systems that may be expected to be much slower on the basis of the different proportion of the water column with respect to the sediment surface. Therefore, a data gap has been identified for the exposure assessment of major photolysis metabolites in the aquatic environment not yet addressed by the available assessment; this data gap was identified by EFSA at the time of producing the conclusion. The necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC) calculations) were carried out for the metabolites IN-JT333, IN-JU873, IN-ML438, IN-KG433, IN-MK643, IN-MK638, IN-KT413, IN-MP819, IN-MS775, IN-KB687, IN-U8E24, IN-UYG24 (up to FOCUS Step 2) using the FOCUS (2001) step 1 and step 2 approach (version 2.1 of the Steps 1–2 in FOCUS calculator). For the active substance indoxacarb, step 3 (FOCUS, 2001) and step 4 calculations were available. The step 4 calculations followed the FOCUS (2007) guidance, with no-spray drift buffer zones with vegetative buffer strips of up to 10 m (maize) or 20 m (lettuce) being implemented. Calculations for metabolite IN-U8E24 need to be revisited once the identified data gaps are fulfilled.

The potential for groundwater contamination by indoxacarb and metabolites IN-JT333, IN-JU873, IN-ML438, IN-KG433, IN-MK643, IN-MK638, IN-KT413 and IN-KB687 was assessed by calculation of 80th percentile of 20 years annual average concentrations at 1 m depth with FOCUS GW PELMO 5.5.3 and PEARL 4.4.4 models. The parametric drinking water limit of 0.1 μg/L was not exceeded by any of these substances for any of the eight relevant scenarios for maize, or any of the six relevant scenarios for cabbage (as surrogate of lettuce, either for early or late season applications). Calculations for metabolite IN-U8E24 need to be revisited once the identified data gaps are fulfilled.

The applicant did not provide appropriate information to address the effect of water treatment processes on the nature of the residues that might be present in surface water and groundwater, when surface water or groundwater is abstracted for drinking water. This has led to the identification of a data gap (see Section 7) and results in the consumer risk assessment not being finalised (see Section 9).

The PEC in soil, surface water, sediment and groundwater covering the representative uses assessed can be found in Appendix A of this conclusion. Exposure assessment for metabolite IN-U8E24 needs to be revisited once studies providing reliable degradation and adsorption endpoints become available.

5. Ecotoxicology

The risk assessment was based on the following documents: European Commission (2002a,b), SETAC (2001), EFSA (2009), EFSA PPR Panel (2013) and EFSA (2013). According to Regulation (EU) No. 283/2013, data should be provided regarding the acute and chronic toxicity to honeybees and data to address the development of honeybee brood and larvae. As the European Commission (2002a) does not provide a risk assessment scheme which is able to use the chronic toxicity data for adult honeybees and the honeybee brood, when performing the risk assessment according to European Commission (2002a), the risk to adult honeybees from chronic toxicity and the risk to bee brood could not be finalised due to the lack of a risk assessment scheme. Therefore, EFSA (2013) was used for risk assessment in order to reach a conclusion for the representative uses.

The specification of the current commercial product defines indoxacarb (DPX-KN128) as the almost pure active *S*-isomer. However, the product was previously commercialised as a mixture of isomers and has been developed based on studies performed with two main mixtures DPX-JW062 (racemic) and DPX-MP062 (75*S*:25*R*). All studies are considered relevant for the purpose of the renewal.

The risk assessment (acute and long-term) to **birds** via dietary exposure resulted in a low risk at the lower tier levels for all representative uses for indoxacarb and metabolite IN-JT333. The risk from exposure via contaminated water was concluded to be high for the representative use on lettuce in the leaf scenario (data gap). A low risk for birds was concluded from secondary poisoning for all representative uses for indoxacarb.

The acute risk for **mammals** was low at lower tier level for all representative uses of indoxacarb, while for metabolite IN-JT333, the acute risk was low for maize, but a high acute risk was identified for small herbivorous mammals in lettuce. The refined risk was low for lettuce for metabolite IN-JT333.

The long-term risk to mammals was high for small herbivorous mammals for indoxacarb for the representative uses on maize, and for small insectivorous, small and large herbivorous, and small omnivorous mammals for the representative uses on lettuce. No acceptable refinements were available except for large herbivorous mammals, and therefore, a high long-term risk was concluded for all representative uses for indoxacarb and a data gap to address the long-term risk for mammals was identified (see Section 7), leading also to a critical area of concern. The risk from exposure via contaminated water for mammals for indoxacarb and metabolite IN-JT333 was concluded to be low for all representative uses. A high risk for earthworm-eating mammals was concluded from secondary poisoning for all representative uses of indoxacarb, and therefore, a data gap was identified, leading to a critical area of concern (see Sections 7 and 9).

The estimated bioconcentration factor (BCF) values for metabolites with log $K_{ow} \geq 3$ were not sufficiently robust, and therefore, a data gap was identified for the risk assessment from secondary poisoning for birds and mammals for metabolites IN-JT333, IN-JU873, IN-ML438, IN-MP819, IN-MS775 and IN-U8E24 (see Section 7).

Valid endpoints addressing the effects on **aquatic organisms** of indoxacarb were available for fish (acute and chronic), aquatic invertebrates (acute and chronic), algae and sediment dwellers. By using the available and agreed endpoints in the risk assessment, a low acute and chronic risk to fish, aquatic invertebrates and algae was concluded for all representative uses of indoxacarb, using predicted

environmental concentration in surface water (PEC_{sw}) calculated with FOCUS Steps 1–2 and 3. For the representative uses in maize, the long-term risk to sediment-dwelling organisms is considered low at FOCUS Step 4 when considering 10 m buffer zone and 10 m vegetated buffer strip. For the representative uses in lettuce, the long-term risk to sediment-dwelling organisms is considered low at FOCUS Step 4 when considering 20 m buffer zone and 20 m vegetated buffer strip.

Valid endpoints addressing the acute toxicity to fish, aquatic invertebrates and algae were available for the surface water metabolites IN-JT333, IN-JU873, IN-KT413, IN-MK638, IN-MK643, IN-KB687, IN-MP819, IN-MS775, IN-U8E24 and IN-UYG24. For metabolite IN-KG433, data on toxicity to algae were not available and for metabolite IN-ML438 data on toxicity to fish, aquatic invertebrates and algae were not available; therefore, the risk assessment was conducted by considering these metabolites as 10 times more toxic than the parent. The risk to aquatic organisms from the pertinent indoxacarb metabolites is considered low at FOCUS Steps 1 and 2 for all representative uses.

Valid endpoints addressing the toxicity to sediment dwellers were available for metabolites IN-JT333, IN-KG433, IN-KT413, IN-MP819, IN-MS775 and IN-U8E24. The risk to sediment-dwelling organisms from these metabolites was considered low at FOCUS Steps 1 and 2 for all representative uses. For metabolite IN-U8E24, low risk was concluded as its toxicity to sediment dwellers was very low compared to the toxicity of the parent compound. Endpoints addressing the toxicity to sediment dwellers were not available for metabolites IN-JU873, IN-MK638, IN-MK643, IN-KB687 and IN-ML438. Based on a screening assessment, a low risk could not be concluded and a data gap was identified to finalise the risk assessment (see Sections 7 and 9).

A data gap was identified for the aquatic risk assessment for the aqueous photolysis metabolites IN-MF014, IN-C0639, IN-MA573 and IN-MH304, leading to an issue not finalised (see Section 4).

A risk assessment for honeybees, performed according to European Commission (2002a), indicated a high acute oral and contact risk to honeybees for all representative uses. A risk assessment for **honeybees** was performed by the applicant according to EFSA (2013), but it was not assessed by the RMS. A low risk to larvae (chronic) honeybees was concluded at the screening step for all representative uses of indoxacarb. High risk to adult (acute oral, acute contact and chronic) honeybees was concluded from exposure to indoxacarb at the first tier for the treated crops and weeds scenarios for all uses. The risk from the exposure scenarios field margins, adjacent crop and next crop was concluded to be low for all uses. Semifield and tunnel studies conducted with 'Indoxacarb 150 g/L EC' have shown potential risk to bees under actual conditions of use in maize. A low risk was identified from exposure via contaminated water.

No assessment was available for sublethal effects on hypopharyngeal glands (i.e. HPG) (data gap). No data were provided for the assessment of accumulative effects and for the full assessment of the risk to wild bees. No information was available regarding plant metabolites occurring in pollen and nectar for the representative uses on maize (data gap).

Tier 1 studies were available with the two standard **non-target arthropod** species. Based on the available data, low risk was identified for *Typhlodromus pyri* (infield and off-field) and for *Aphidius rhopalosiphi* (off-field) at tier 1. Infield risk was low for *A. rhopalosiphi* considering the results of an aged residue study at tier 1 for all representative uses. This conclusion was supported by the available higher tier studies with *A. rhopalosiphi* and additional species.

Toxicity data with **earthworms** and other **soil macroorganisms** were available with the active substance and the pertinent soil metabolites. For metabolites IN-ML438 and IN-U8E24, data were not available; therefore, the risk assessment was conducted by considering these metabolites as 10 times more toxic than the parent. Data with the representative formulation were also available. Low risk to earthworms and other soil macroorganisms was concluded for all representative uses.

Low risk to **soil microorganisms**, **non-target terrestrial plants** and **biological methods of sewage treatment** was concluded.

With regard to the endocrine disruption potential, as discussed in Section 2, it is unlikely that indoxacarb has endocrine disrupting properties in mammals; however, no firm conclusion can be drawn regarding fish, birds and amphibians.

6. Overview of the risk assessment of compounds listed in residue definitions triggering assessment of effects data for the environmental compartments (Tables 1–4)

Table 1: Soil

Compound (name and/or code)	Persistence	Ecotoxicology
Indoxacarb	Medium to high (DT_{50} = 65.3–231 days)	Low risk to soil organisms
IN-JT333 (IN-KN125)	Moderate to high (DT_{50} = 19.6–147.5 days)	Low risk to soil organisms
IN-KG433	Low to moderate (DT_{50} = 3.95–17.4 days)	Low risk to soil organisms
IN-KT413	Very low to low (DT_{50} = 0.8–10.4 days)	Low risk to soil organisms
IN-JU873	Moderate to high (DT_{50} = 24.8–103.5 days)	Low risk to soil organisms
IN-ML438	Medium to high (DT_{50} = 80.9–186.5 days)	Low risk to soil organisms
IN-MK638	Low to moderate persistence (DT_{50} = 4.8–17.3 days)	Low risk to soil organisms
IN-KB687	Very low (DT_{50} = 0.56–0.67 days)	Low risk to soil organisms
IN-MK643	High (DT_{50} = 123.3–314.2 days)	Low risk to soil organisms
IN-U8E24	Data gap	Low risk to soil organisms

DT50: period required for 50% dissipation.

Table 2: Groundwater

Compound (name and/or code)	Mobility in soil	> 0.1 µg/L at 1 m depth for the representative uses[a]	Pesticidal activity	Toxicological relevance
Indoxacarb	Immobile to slight	FOCUS GW: No	Yes	Yes
IN-JT333	Immobile	FOCUS GW: No	No data	Unlikely to be genotoxic
IN-KG433	Medium	FOCUS GW: No	No data	Unlikely to be genotoxic
IN-KT413	Medium	FOCUS GW: No	No data	Unlikely to be genotoxic
IN-JU873	Medium to high	FOCUS GW: No	No data	No data
IN-ML438	Immobile	FOCUS GW: No	No data	No data
IN-MK638	Medium to high	FOCUS GW: No	No data	No data
IN-KB687	Medium	FOCUS GW: No	No data	Unlikely to be genotoxic
IN-MK643	Medium	FOCUS GW: No	No data	No data
IN-U8E24	Data gap	Data gap	No data	No data

FOCUS: Forum for the Co-ordination of Pesticide Fate Models and their Use; GW: ground water.
(a): FOCUS scenarios or relevant lysimeter.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Indoxacarb (water and sediment)	Low risk to aquatic organisms
IN-JT333 (water and sediment)	Low risk to aquatic organisms
IN-KG433 (water and sediment)	Low risk to aquatic organisms
IN-KT413 (water and sediment)	Low risk to aquatic organisms
IN-JU873 (water and sediment, soil metabolite)	Data gap
IN-ML438 (water and sediment, soil metabolite)	Data gap
IN-MK638 (water and sediment, soil metabolite)	Data gap
IN-KB687 (water and sediment, soil and aqueous photolysis metabolite)	Data gap
IN-MK643 (water and sediment, soil metabolite)	Data gap
IN-MP819 (water and sediment)	Low risk to aquatic organisms
IN-MS775 (water and sediment)	Low risk to aquatic organisms
IN-U8E24 (water and sediment, soil metabolite)	Low risk to aquatic organisms
IN-UYG24 (water)	Low risk to aquatic organisms
IN-MF014 (aqueous photolysis)	Data gap
IN-C0639 (aqueous photolysis)	Data gap
IN-MA573 (aqueous photolysis)	Data gap
IN-MH304 (aqueous photolysis)	Data gap

Table 4: Air

Compound (name and/or code)	Toxicology
Indoxacarb	LC_{50} rat = 4.2 mg/L air per 4 h (nose-only)

LC_{50}: lethal concentration, median.

7. Data gaps

This is a list of data gaps identified during the peer review process, including those areas in which a study may have been made available during the peer review process but not considered for procedural reasons (without prejudice to the provisions of Article 56 of Regulation (EC) No 1107/2009 concerning information on potentially harmful effects).

- An appropriate literature search for relevant metabolites has to be provided by the applicant in accordance with the EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011a) (relevant for Sections 2, 3 and 4). In addition, the applicant to provide a new literature search analysis with more appropriate criteria for relevance and reliability (relevant for Section 4).
- Efficiency of the extraction procedure used in the analytical methods for the determination of residues in dry commodity (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- ILV of the monitoring method for determination of residues in fat matrix (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- A comparative *in vitro* metabolism study should be provided (relevant for all representative uses evaluated; submission date proposed by the applicant: ongoing; see Section 2).
- Confined rotational crops metabolism studies addressing the potential uptake and fate of indoxacarb and of its metabolites: IN-MK643, IN-ML438, IN-JT333 and IN-JU873 in leafy crops, small grain crops and root crops and to enable the calculation of reliable soil/plant transfer factors for the parent indoxacarb and all relevant compounds (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Sufficient NEU and SEU GAP-compliant residue trials on maize grain and forage and conducted with the DPX-KN128 150EC formulation (with a possible extrapolation from immature maize grain to sweet corn) (relevant for the representative uses on maize and sweet corn; submission date proposed by the applicant: unknown; see Section 3).
- Sufficient NEU and SEU bridging residue data on lettuce with the representative DPX-KN128 150EC formulation should be provided to demonstrate that residues are similar from the EC and WG formulations (relevant for the representative use on lettuce; submission date proposed by the applicant: unknown; see Section 3).
- The status of the study to verify the occurrence and confirmation that the structure of IN-VRN79 corresponds to metabolite 'F' in the poultry metabolism study (relevant for the representative use on maize; submission date proposed by the applicant: unknown; see Section 3).
- Determination of residues of indoxacarb and/or its degradation products in pollen and bee products for human consumption resulting from residues taken up by honeybees from maize at blossom (relevant for the representative use on maize; submission date proposed by the applicant: unknown; see Section 3).
- The applicant to provide the soil degradation and adsorption studies and exposure assessment for metabolite IN-U8E24 (relevant for all representative uses evaluated; submission date proposed by the applicant: end of 2017; see Section 4).
- The applicant to further investigate identification and characterisation of the unidentified polar fraction and the identity of metabolite IN-ML437-OH in the study of Singles, 2002 in France (2017). A new study, DuPont-48964, has been initiated, the study is expected to be finalised by June 2019 (relevant for all representative uses evaluated; submission date proposed by the applicant: June 2019; see Section 4).
- The applicant to provide exposure assessment for the aquatic environment for the aqueous photolysis metabolites: IN-MF014 (max: 37.6% AR), IN-C0639 (max: 10.2% AR), IN-MA573 (max: 19.9% AR) and IN-MH304 (max: 32.3% AR) (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 4).
- The applicant to provide information to address the degradation of indoxacarb in acidic water sediment systems (relevant for all representative uses evaluated; no submission date proposed by the applicant; see Section 4).
- The applicant to provide appropriate information to address the effect of water treatment processes on the nature of the residues that might be present in surface water and groundwater, when surface water or groundwater is abstracted for drinking water (for instance investigation of the processes of ozonation and chlorination would appear appropriate); (relevant for all representative uses evaluated; no submission date proposed by the applicant; see Section 4).

- Further information to refine the risk for birds from consumption of contaminated water is needed (relevant for the representative uses on lettuce; no submission date proposed by the applicant; see Section 5).
- Further information to refine the long-term risk for small herbivorous mammals for the representative uses on maize and for the small insectivorous, small herbivorous and small omnivorous mammals for the representative uses on lettuce is needed for indoxacarb (relevant for all representative uses evaluated; no submission date proposed by the applicant; see Section 5).
- Further information to refine the risk assessment for birds and wild mammals from secondary poisoning for metabolites IN-JT333, IN-JU873, IN-ML438, IN-MP819, IN-MS775 and IN-U8E24 (relevant for all representative uses evaluated; no submission date proposed by the applicant; see Section 5).
- Further information to refine the risk assessment for earthworm-eating mammals from secondary poisoning for all representative uses of indoxacarb. A worm bioconcentration study to obtain a measured BCF value will be started in late 2017 (relevant for all representative uses evaluated; submission date proposed by the applicant: late 2018; see Section 5).
- Information to assess the risk for the aqueous photolysis metabolites IN-MF014, IN-C0639, IN-MA573 and IN-MH304 (relevant for all representative uses evaluated; no submission date proposed by the applicant; see Section 5).
- Information to assess the risk to sediment dwellers for metabolites IN-JU873, IN-MK638, IN-MK643, IN-KB687 and IN-ML438 (relevant for all representative uses evaluated; no submission date proposed by the applicant; see Section 5).
- Based on EFSA (2013), suitable data to address the risk of sublethal effects (i.e. HPG) to honeybees from exposure to indoxacarb are needed (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Information to assess the risk to honeybees for plant metabolites occurring in pollen and nectar (relevant for the representative uses on maize; submission date proposed by the applicant: unknown; see Section 5).

8. Particular conditions proposed to be taken into account to manage the risk(s) identified

- Use of PPE (gloves and coverall) is required for operators applying 'Indoxacarb 150 g/L EC' in maize, sweet corn and lettuce, in order to have a predicted exposure below the AOEL (see Section 2).
- Use of PPE (gloves) is required for workers re-entering maize and sweet corn fields after two applications, in order to have a predicted exposure below the AOEL (see Section 2).
- A low risk was concluded for aquatic organisms from 'Indoxacarb 150 g/L EC' provided that mitigation measures such as a 10 m buffer zone and 10 m vegetated buffer strip are maintained in maize, and a 20 m buffer zone and 20 m vegetated buffer strip are maintained in lettuce (see Section 5).

9. Concerns

9.1. Issues that could not be finalised

An issue is listed as 'could not be finalised' if there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the uniform principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011[4] and if the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

An issue is also listed as 'could not be finalised' if the available information is considered insufficient to conclude on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

[4] Commission Regulation (EU) No 546/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards uniform principles for evaluation and authorisation of plant protection products. OJ L 155, 11.6.2011, p. 127–175.

1) The need for further tests and risk assessment to unique human metabolites could not be finalised whilst an *in vitro* comparative metabolism study was not submitted (see Section 2).
2) The consumer dietary risk assessment cannot be finalised considering the identified data gaps. Furthermore, an acute intake concern was identified for lettuce (IESTI: 457.4% of ARfD, German child) (see Section 3).
3) The consumer risk assessment cannot be finalised due to the lack of sufficient and reliable information on the effect of water treatment processes on the nature of the residues (see Section 4).
4) Exposure assessment in relation to groundwater cannot be finalised for the soil metabolite IN-U8E24.
5) Risk assessment for birds and wild mammals from secondary poisoning cannot be finalised for relevant metabolites (see Section 5).
6) Risk assessment for sediment dwelling organisms for metabolites IN-JU873, IN-MK638, IN-MK643, IN-KB687 and IN-ML438 cannot be finalised (see Section 5).
7) Risk assessment in relation to the aquatic environment cannot be finalised with respect to the major photolysis metabolites IN-MF014, IN-C0639, IN-MA573 and IN-MH304 (see Sections 4 and 5).

9.2. Critical areas of concern

An issue is listed as a critical area of concern if there is enough information available to perform an assessment for the representative uses in line with the uniform principles in accordance with Article 29 (6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011, and if this assessment does not permit the conclusion that, for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern if the assessment at the higher tier level could not be finalised due to lack of information, and if the assessment performed at the lower tier level does not permit the conclusion that, for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern if, in the light of current scientific and technical knowledge using guidance documents available at the time of application, the active substance is not expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

8) High long-term risk was concluded for wild mammals for all representative uses of indoxacarb (see Section 5).
9) High risk was concluded for earthworm-eating mammals from secondary poisoning for all representative uses of indoxacarb (see Section 5).
10) High acute risk was concluded for honeybees for all representative uses of indoxacarb (see Section 5).

9.3. Overview of the concerns identified for each representative use considered

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in Section 8, has been evaluated as being effective, then 'risk identified' is not indicated in Table 5.)

Table 5: Overview of concerns

Representative use		Maize, sweet corn (EU critical GAP)	Maize (grain and forage (SEU)	Maize (grain and forage) (CEU + NEU)	Sweet corn (SEU)	Sweet corn (CEU+ NEU)	Lettuce (EU critical GAP)	Lettuce (SEU except FR)
Operator risk	Risk identified							
	Assessment not finalised							
Worker risk	Risk identified						X	X
	Assessment not finalised							
Resident/ bystander risk	Risk identified							
	Assessment not finalised							
Consumer risk	Risk identified						X[2]	X[2]
	Assessment not finalised	X[2,3]	X[2,3]	X[2,3]	X[2,3]	X[2,3]	X[2,3]	X[2,3]
Risk to wild non-target terrestrial vertebrates	Risk identified	X[8,9]	X[8,9]	X[8,9]	X[8,9]	X[8,9]	X[8,9]	X[8,9]
	Assessment not finalised	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]*	X[10]*
	Assessment not finalised							
Risk to aquatic organisms	Risk identified							
	Assessment not finalised	X[6,7]	X[6,7]	X[6,7]	X[6,7]	X[6,7]	X[6,7]	X[6,7]
Groundwater exposure to active substance	Legal parametric value breached							
	Assessment not finalised							
Groundwater exposure to metabolites	Legal parametric value breached[(a)]							
	Parametric value of 10 µg/L[(b)] breached							
	Assessment not finalised	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]

GAP: Good Agricultural Practice; SEU: southern Europe; CEU: central Europe; NEU: northern Europe.
Columns are grey if no safe use can be identified. The superscript numbers relate to the numbered points indicated in Sections 9.1 and 9.2. Where there is no superscript number, see Sections 2–6 for further information.
*: On the basis of European Commission guidance (2002a), this concern is only applicable for the use in lettuce for seed production.
(a): When the consideration for classification made in the context of this evaluation under Regulation (EC) No 1107/2009 is confirmed under Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008.
(b): Value for non-relevant metabolites prescribed in SANCO/221/2000-rev. 10 final, European Commission, 2003.

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Abbreviations

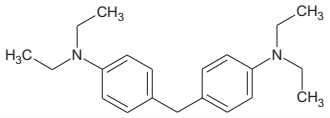
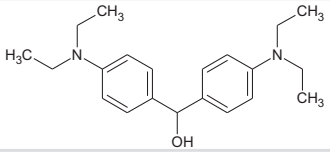
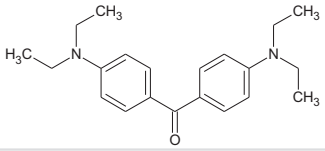
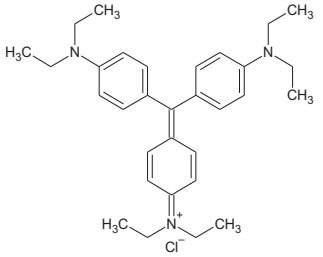
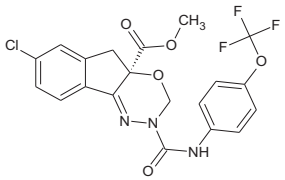
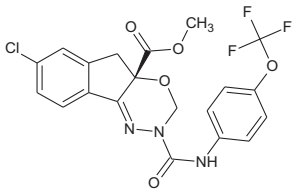
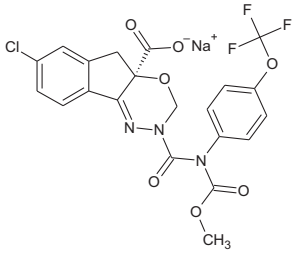
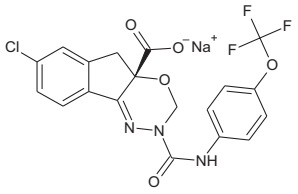
AAOEL	acute acceptable operator exposure level
ADI	acceptable daily intake
AOEL	acceptable operator exposure level
AR	applied radioactivity
ARfD	acute reference dose
BCF	bioconcentration factor
bw	body weight
CEU	central Europe
co-RMS	co-rapporteur Member State
CXLs	codex maximum residue limits
DT_{50}	period required for 50% dissipation (define method of estimation)
EC	emulsifiable concentrate
EEC	European Economic Community
EUROPOEM	European Predictive Operator Exposure Model
FAO	Food and Agriculture Organization of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	Good Agricultural Practice
HPG	hypopharyngeal glands
IESTI	international estimated short-term intake
ILV	independent laboratory validation
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
K_{ow}	*n*-octanol/water partition coefficient
LC_{50}	lethal concentration, median
LC–MS/MS	liquid chromatography with tandem mass spectrometry
LOAEL	lowest observable adverse effect level
LOQ	limit of quantification
MRL	maximum residue level
MS	mass spectrometry
NEU	northern Europe
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
PBI	plant-back interval
PEC	predicted environmental concentration
PEC_{air}	predicted environmental concentration in air
PEC_{gw}	predicted environmental concentration in groundwater
PEC_{sed}	predicted environmental concentration in sediment
PEC_{soil}	predicted environmental concentration in soil
PEC_{sw}	predicted environmental concentration in surface water
PPE	personal protective equipment
RAR	Renewal Assessment Report
RMS	rapporteur Member State
SEU	southern Europe
SMILES	simplified molecular-input line-entry system
TMDI	theoretical maximum daily intake
TRR	total radioactive residue

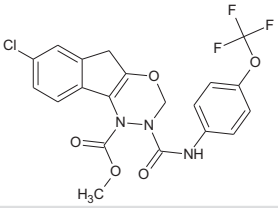
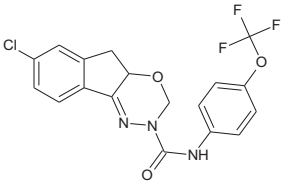
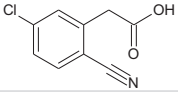
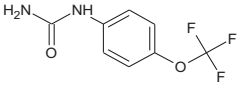
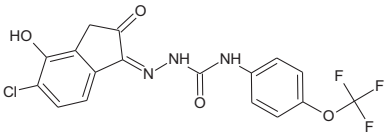
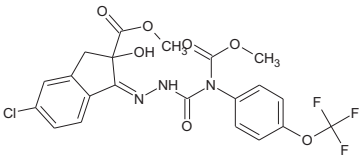
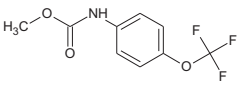
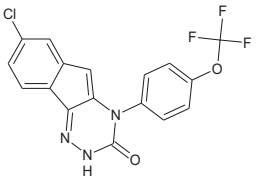
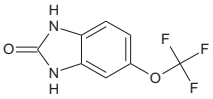
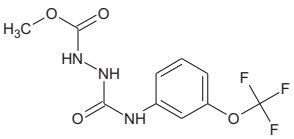
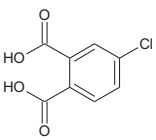
UF	uncertainty factor
WG	water-dispersible granule
WHO	World Health Organization

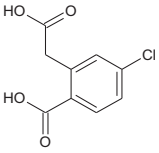
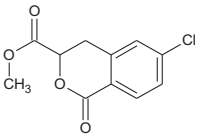
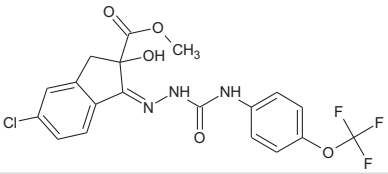
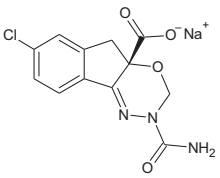
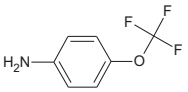
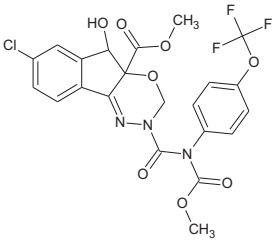
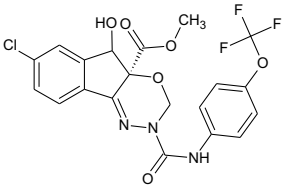
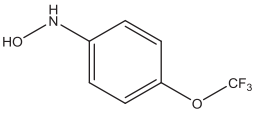
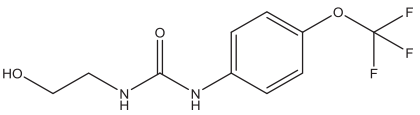
Appendix A – List of endpoints for the active substance and the representative formulation

Appendix A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2018.5140

Appendix B – Used compound codes

Code/trivial name	Chemical name/SMILES notation	Structural formula
bis(diethylamino) diphenylmethane (IN-06439)	4,4′-methylenebis(*N*,*N*-diethylaniline) CCN(CC)c1ccc(cc1)Cc2ccc(cc2)N(CC)CC	
bis(4-Diethylaminophenyl) methanol (IN-R1T94)	bis[4-(diethylamino)phenyl]methanol CCN(CC)c1ccc(cc1)C(O)c2ccc(cc2)N(CC)CC	
bis(Diethylamino) benzophenone (IN-C0800)	bis[4-(diethylamino)phenyl]methanone CCN(CC)c1ccc(cc1)C(=O)c2ccc(cc2)N(CC)CC	
tris(*p*-(diethylamino) phenyl)methylium chloride (IN-J1063)	4-{bis[4-(diethylamino)phenyl]methylidene}-*N*,*N*-diethylcyclohexa-2,5-dien-1-iminium chloride [Cl-].CC/[N+](CC)=C1\C=C/C(C=C1)=C(/c2ccc(cc2)N(CC)CC)c3ccc(cc3)N(CC)CC	
IN-JT333	methyl (4a*R*)-7-chloro-2-{[4-(trifluoromethoxy)phenyl]carbamoyl}-2,5-dihydroindeno[1,2-*e*][1,3,4]oxadiazine-4a(3*H*)-carboxylate FC(F)(F)Oc1ccc(cc1)NC(=O)N2N=C3c4ccc(Cl)cc4C[C@]3(OC2)C(=O)OC	
IN-KN125	methyl (4a*S*)-7-chloro-2-{[4-(trifluoromethoxy)phenyl]carbamoyl}-2,5-dihydroindeno[1,2-*e*][1,3,4]oxadiazine-4a(3*H*)-carboxylate FC(F)(F)Oc1ccc(cc1)NC(=O)N2N=C3c4ccc(Cl)cc4C[C@@]3(OC2)C(=O)OC	
IN-KT413	sodium (4a*R*)-7-chloro-2-{(methoxycarbonyl)[4-(trifluoromethoxy)phenyl]carbamoyl}-2,5-dihydroindeno[1,2-*e*][1,3,4]oxadiazine-4a(3*H*)-carboxylate [Na+].FC(F)(F)Oc1ccc(cc1)N(C(=O)OC)C(=O)N2N=C3c4ccc(Cl)cc4C[C@]3(OC2)C([O-])=O	
IN-U8E24	sodium (4a*S*)-7-chloro-2-{[4-(trifluoromethoxy)phenyl]carbamoyl}-2,5-dihydroindeno[1,2-*e*][1,3,4]oxadiazine-4a(3*H*)-carboxylate [Na+].FC(F)(F)Oc1ccc(cc1)NC(=O)N2N=C3c4ccc(Cl)cc4C[C@@]3(OC2)C([O-])=O	

Code/trivial name	Chemical name/SMILES notation	Structural formula
IN-MP819	Methyl 7-chloro-2-{[4-(trifluoromethoxy)phenyl] carbamoyl}-2,3-dihydroindeno[1,2-e][1,3,4] oxadiazine-1(5*H*)-carboxylate FC(F)(F)Oc1ccc(cc1)NC(=O)N4COC=3Cc2cc(Cl) ccc2C=3N4C(=O)OC	
IN-MS775	7-chloro-*N*-[4-(trifluoromethoxy)phenyl]-4a,5-dihydroindeno[1,2-e][1,3,4]oxadiazine-2(3*H*)-carboxamide FC(F)(F)Oc1ccc(cc1)NC(=O)N2N=C3c4ccc(Cl) cc4CC3OC2	
IN-U8F52	(5-chloro-2-cyanophenyl)acetic acid N#Cc1ccc(Cl)cc1CC(=O)O	
IN-MK638	*N*-[4-(trifluoromethoxy)phenyl]urea FC(F)(F)Oc1ccc(cc1)NC(N)=O	
IN-ML437-OH	(2*Z*)-2-(5-chloro-4-hydroxy-2-oxo-2,3-dihydro-1*H*-inden-1-ylidene)-*N*-[4-(trifluoromethoxy) phenyl]hydrazine-1-carboxamide FC(F)(F)Oc1ccc(cc1)NC(=O)N\N=C2\c3ccc(Cl)c (O)c3CC2=O	
IN-KG433	methyl (1*Z*,2*RS*)-5-chloro-2-hydroxy-1-(2-{(methoxycarbonyl)[4-(trifluoromethoxy)phenyl] carbamoyl}hydrazinylidene)-2,3-dihydro-1*H*-indene-2-carboxylate FC(F)(F)Oc1ccc(cc1)N(C(=O)OC)C(=O)N\N=C2 \c3ccc(Cl)cc3CC2(O)C(=O)OC	
IN-KB687	methyl [4-(trifluoromethoxy)phenyl]carbamate FC(F)(F)Oc1ccc(cc1)NC(=O)OC	
IN-ML438	7-chloro-4-[4-(trifluoromethoxy)phenyl]-2,4-dihydro-3*H*-indeno[2,1-e][1,2,4]triazin-3-one FC(F)(F)Oc1ccc(cc1)N2C(=O)NN=C3c4ccc(Cl) cc4C=C23	
IN-MK643	5-(trifluoromethoxy)-1,3-dihydro-2*H*-benzimidazol-2-one FC(F)(F)Oc1ccc2NC(=O)Nc2c1	
IN-MF014	methyl 2-{[3-(trifluoromethoxy)phenyl] carbamoyl}hydrazine-1-carboxylate FC(F)(F)Oc1cccc(c1)NC(=O)NNC(=O)OC	
IN-C0639 Dicarboxylic acid derived of IN-MA573 (aqueous photodegradation)	4-chlorobenzene-1,2-dicarboxylic acid OC(=O)c1ccc(Cl)cc1C(=O)O	

Code/trivial name	Chemical name/SMILES notation	Structural formula
IN-MA573	2-(carboxymethyl)-4-chlorobenzoic acid OC(=O)c1ccc(Cl)cc1CC(=O)O	
IN-MH304	methyl 6-chloro-1-oxo-3,4-dihydro-1*H*-2-benzopyran-3-carboxylate O=C(OC)C1Cc2cc(Cl)ccc2C(=O)O1	
IN-JU873	methyl (1*Z*,2*RS*)-5-chloro-2-hydroxy-1-(2-{[4-(trifluoromethoxy)phenyl]carbamoyl}hydrazinylidene)-2,3-dihydro-1*H*-indene-2-carboxylate FC(F)(F)Oc1ccc(cc1)NC(=O)N\N=C2\c3ccc(Cl)cc3CC2(O)C(=O)OC	
IN-UYG24	sodium (4a*S*)-2-carbamoyl-7-chloro-2,5-dihydroindeno[1,2-e][1,3,4]oxadiazine-4a(3*H*)-carboxylate [Na+].[O-]C(=O)[C@@]23Cc1cc(Cl)ccc1C3=NN(CO2)C(N)=O	
IN-P0036	4-(trifluoromethoxy)aniline FC(F)(F)Oc1ccc(N)cc1	
5-OH-DPX-JW062	Methyl (4a*RS*,5*RS*)-7-chloro-5-hydroxy-2-{(methoxycarbonyl)[4-(trifluoromethoxy)phenyl]carbamoyl}-2,5-dihydroindeno[1,2-e][1,3,4]oxadiazine-4a(3*H*)-carboxylate FC(F)(F)Oc1ccc(cc1)N(C(=O)OC)C(=O)N3N=C4c2ccc(Cl)cc2C(O)C4(OC3)C(=O)OC	
5-OH-IN-JT333	methyl (4a*S*,5*RS*)-7-chloro-5-hydroxy-2-{[4-(trifluoromethoxy)phenyl]carbamoyl}-2,5-dihydroindeno[1,2-e][1,3,4]oxadiazine-4a(3*H*)-carboxylate FC(F)(F)Oc1ccc(cc1)NC(=O)N3N=C4c2ccc(Cl)cc2C(O)[C@]4(OC3)C(=O)OC	
IN-MT713	*N*-(4-(trifluoromethoxy)phenyl)hydroxylamine ONC1=CC=C(OC(F)(F)F)C=C1	
IN-MN470	1-(2-hydroxyethyl)-3-(4-(trifluoromethoxy)phenyl)urea O=C(NCCO)Nc1ccc(OC(F)(F)F)cc1	
IN-VRN79 (Metabolite'F')		Structure currently unknown.

SMILES: simplified molecular-input line-entry system.