European Commission

Draft Renewal Assessment Report prepared according to the Commission Regulation (EC) N° 1107/2009

INDOXACARB

Volume 1

Rapporteur Member State: France
Co-Rapporteur Member State: Spain

Version History

When	What
2016-12	Initial RAR

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Level 1

INDOXACARB

1. STATEMENT OF SUBJECT MATTER AND PURPOSE FOR WHICH THIS REPORT HAS BEEN PREPARED AND BACKGROUND INFORMATION ON THE APPLICATION

1.1. CONTEXT IN WHICH THIS DRAFT ASSESSMENT REPORT WAS PREPARED

1.1.1. Purpose for which the draft assessment report was prepared

This renewal assessment report has been prepared in accordance with Commission Regulation (EC) No 844/2012 and Guidance Document SANCO/2012/11251 rev. 4 in order to evaluate the supplementary dossier submitted by DuPont de Nemours (Deutschland) GmbH, and to allow a decision on the renewal of the approval of the active substance Indoxacarb under Commission Regulation (EC) No 1107/2009.

In parallel of this Annex I Renewal dossier, the applicant submitted confirmatory data requested during the review of MRL for Indoxacarb (see, Commission Regulation (EU) No 668/2013 and the EFSA Reasoned Opinion (EFSA Journal 2011;9(8):2343)) conducted in the framework of Art. 12 of Regulation 396/2005. These data were assessed and presented in the Appendix to Volume 3 B7-CA of this Renewal Assessment Report (RAR).

1.1.2. Arrangements between rapporteur Member State and co-rapporteur Member State

According to Commission Regulation (EU) No 686/2012 France was designated Rapporteur Member State (RMS) and Spain assigned as Co-Rapporteur Member State (Co-RMS).

France, as RMS, evaluated the dossier submitted by the applicants and draft the Renewal Assessment Report for all the sections whereas, Spain, as Co-RMS, conducted a pre-peer review of this report. Any deviating views on critical issues between the RMS and the Co-RMS have been reported in Volume 1 Level 3 section 3.1.9.

1.1.3. EU Regulatory history for use in Plant Protection Products

In October 1997, Dupont de Nemours, submitted an application for the inclusion of the new active substance Indoxacarb in Annex I of the Directive 91/414/EEC. The Netherland was designated RMS to carry out the detailed examination of the dossier and report the conclusions to the Commission.

The draft assessment reports was submitted on February 2000 to the Commission and then reviewed by the Member States and the Commission within the Standing Committee on the Food Chain and Animal Health. The review was finalised on 23 September 2005 in the format of the Commission review report (Indoxacarb SANCO/1408/2001 – rev.3, dated on 23 September 2005). Indoxacarb was listed in Annex I of Directive 91/414/EEC on 27th January 2006 (Commission Directive 2006/10/EC) with the following specific provisions:
Only uses as insecticide may be authorised.
For the implementation of the uniform principles of Annex VI, the conclusions of the review report on indoxacarb, and in particular Appendices I and II thereof, as finalised in the Standing Committee on the Food Chain and Animal Health on 23 September 2005 shall be taken into account.
In this overall assessment Member States must pay particular attention to the protection of aquatic organisms.
Conditions of use should include risk mitigation measures, where appropriate.
By Commission Regulation 533/2013/EC, the expiry date of approval of Indoxacarb, initially on 31 March 2016, was extended to 31 October 2017.

According to Article 18(1)b of Regulation (EC) 396/2005, default EU MRLs have been established in 2008 (Commission Regulation (EU) No. 149/2008). According to art.12 of (EC) 396/2005, EFSA has

reviewed the existing MRLs for Indoxacarb (EFSA Journal 2011;9(8):2343) and these MRLs have been adopted under Commission Regulation (Commission Regulation (EU) No. 668/2013).

1.1.4. Evaluations carried out under other regulatory contexts

Indoxacarb is currently under Registration Review at US-EPA (Docket N° EPA-HQ-OPP-2013-0367). Indoxacarb was as well evaluated by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) in 2005 (Toxicology and Residue Evaluation), 2007 (Residue Evaluation), 2009 (Toxicology and Residue Evaluation).

1.2. APPLICANT INFORMATION

1.2.1. Name and address of applicant(s) for approval of the active substance

DuPont de Nemours (Deutschland) GmbH
Address: Hugenottenallee 173-175
D-63263 Neu-Isenburg
Germany

1.2.2. Producer or producers of the active substance

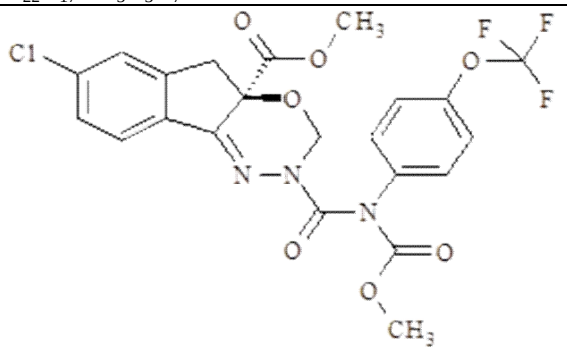
DuPont International Operations Sarl
Confidential information, data are provided in Indoxacarb Volume 4.

1.2.3. Information relating to the collective provision of dossiers

Not applicable, Dupont is the sole data submitter for the Renewal of Indoxacarb

1.3. IDENTITY OF THE ACTIVE SUBSTANCE

1.3.1. Common name proposed or ISO-accepted and synonyms	Indoxacarb
1.3.2. Chemical name (IUPAC and CA nomenclature)	
IUPAC	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
CA	methyl (4aS)-7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4-(trifluoromethoxy)phenyl]amino]carbonyl]indeno[1,2-e][1,3,4]oxadiazine-4a(3H)-carboxylate

1.3.3. Producer's development code number	The following development codes are used in the EU renewal dossier for indoxacarb: • DPX-KN128: The pure insecticidal active isomer (S-isomer) and the technical material for this active substance in the renewal dossier • DPX-MP062 is the development code for the technical material containing approximately 75% DPX KN128 and 25% IN-KN127 (insecticidally inactive enantiomer), used as reference material in Indoxacarb DAR and review report (Indoxacarb SANCO/1408/2001 Rev.3) from 2005. • DPX-JW062 is the development code for the racemic mixture of DPX-KN128 and IN-KN127.
1.3.4. CAS, EEC and CIPAC numbers	
CAS	173584-44-6
EEC	Not available
CIPAC	612
1.3.5. Molecular and structural formula, molecular mass	
Molecular formula	$C_{22}H_{17}ClF_3N_3O_7$
Structural formula	
Molecular mass	527.84 g/mol

1.3.6. Method of manufacture (synthesis pathway) of the active substance	CONFIDENTIAL information – see Volume 4
1.3.7. Specification of purity of the active substance in g/kg	**930 g/kg**
1.3.8. Identity and content of additives (such as stabilisers) and impurities	
1.3.8.1. Additives	CONFIDENTIAL information – see Volume 4
1.3.8.2. Significant impurities	CONFIDENTIAL information – see Volume 4
1.3.8.3. Relevant impurities	Impurity IN-06439 corresponds to "tetraethyl base": <0.0025g/kg (<2.5ppm) Impurity IN-R1T94 corresponds to "tetraethyl hydrol"; <0.0025g/kg (<2.5 ppm) Impurity IN-J1063 corresponds to "tetraethyl ketone"; <0.0018g/kg (<1.8ppm) Impurity IN-C0800 corresponds to "Ethyl violet"; <0.0025g/kg (<2.5ppm) Toluene: 14 g/kg
1.3.9. Analytical profile of batches	CONFIDENTIAL information – see Volume 4

1.4. INFORMATION ON THE PLANT PROTECTION PRODUCT

1.4.1. Applicant	DuPont de Nemours (Deutschland) GmbH ***Address:*** Hugenottenallee 173-175 D-63263 Neu-Isenburg Germany
1.4.2. Producer of the plant protection product	CONFIDENTIAL information – see Volume 4
1.4.3. Trade name or proposed trade name and producer's development code number of the plant protection product	Indoxacarb 150 g/L EC will be sold as Avaunt® EC Avaunt® 15 EC, Avaunt® 150EC, Steward® EC, or Explicit® EC. Company code number: DPX-KN128 150 g/L EC
1.4.4. Detailed quantitative and qualitative information on the composition of the plant protection product	
1.4.4.1. **Composition of the plant protection product**	150 g/L of pure indoxacarb
1.4.4.2. **Information on the active substances**	ISO common name: Indoxacarb CAS N°: 173584-44-6 EC N°: None CIPACN°: 612
1.4.4.3. **Information on safeners, synergists and co-formulants**	CONFIDENTIAL information – see Volume 4
1.4.5. Type and code of the plant protection product	Emulsifiable concentrate (EC)
1.4.6. Function	Insecticide
1.4.7. Field of use envisaged	Agriculture
1.4.8. Effects on harmful organisms	Indoxacarb (=DPX-KN128) is active as a larvicide by stomach and contact routes of entry into the insect. The importance of stomach versus contact action varies with the species and the crop situation. Data from laboratory and field indicates that the product is active on all larval stages of Lepidoptera, together with some activity on some other orders. For certain species the active has ovicidal effect. Paralysis occurs within a few hours of exposure and results in cessation of movement and feeding. Final control takes 1-3 days. The metabolite IN-JT333 also shows insecticidal effects.

1.5. DETAILED USES OF THE PLANT PROTECTION PRODUCT

1.5.1. Details of representative uses

Crop and/or situation (a)	Member State	Product Name	F G I (b)	Pests or group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks (m)
					Type (d-f)	Conc of a.i. g/L (i)	Method kind (f-h)	Growth stage and season (j)	Number min max (k) a) per use b) per crop/ season	Interval between applications (min)	mL product/ ha a) max. rate per appl. b) max. total rate per crop/season	Water l/ha min max	g a.i./ha a) max. rate per appl. b) max. total rate per crop/season		
Maize, Sweet Corn	EU	Indoxacarb 150 g/L EC (DPX-KN128 150 g/L EC)	F	*Ostrinia nubilalis Diabrotica virgifera*	EC	150	hydraulic ground directed boom Note: application must be made from above the crop	BBCH 34-77	a) 2 b) 2	20 days	a) 250 b) 500	100-1000	a) 37.5 b) 75	BBCH 77	EU CRITICAL GAP
Maize (grain and silage)	South Zone	Indoxacarb 150 g/L EC (DPX-KN128 150 g/L EC)	F	*Ostrinia nubilalis Diabrotica virgifera*	EC	150	hydraulic ground directed boom Note: application must be made from above the crop	BBCH 34-77	a) 2 b) 2	20 days	a) 250 b) 500	100-1000	a) 37.5 b) 75	BBCH 77	
Maize (grain and silage)	Central Zone Northern Zone	Indoxacarb 150 g/L EC (DPX-KN128 150 g/L EC)	F	*Ostrinia nubilalis Diabrotica virgifera*	EC	150	hydraulic ground directed boom Note: application must be made from above the crop	BBCH 34-77	a) 2 b) 2	20 days	a) 250 b) 500	200-700	a) 37.5 b) 75	BBCH 77	
Sweet corn	South Zone	Indoxacarb 150 g/L EC (DPX-KN128 150 g/L EC)	F	*Ostrinia nubilalis Diabrotica virgifera*	EC	150	hydraulic ground directed boom	BBCH 34-77	a) 2 b) 2	20 days	a) 250 b) 500	100-1000	a) 37.5 b) 75	3	

							Note: application must be made from above the crop								
Sweet corn	Central Zone Northern Zone	Indoxacarb 150 g/L EC (DPX-KN128 150 g/L EC)	F	*Ostrinia nubilalis* *Diabrotica virgifera*	EC	150	hydraulic ground directed boom Note: application must be made from above the crop	BBCH 34-77	a) 2 b) 2	20 days	a) 250 b) 500	200-700	a) 37.5 b) 75	3	
Lettuce	EU	Indoxacarb 150 g/L EC (DPX-KN128 150 g/L EC)	F	*Autographa gamma* *Chrysodeixis chalcites* *Helicoverpa armigera* *Mythimna unipuncta* *Spodoptera exigua* *Spodoptera littoralis*	EC	150	hydraulic ground directed boom	BBCH 13-49 Seed crops BBCH 13-59	a) 4 b) 4	7 days	a) 250 b) 1000	200-1000	a) 37.5 b) 150	1	EU CRITICAL GAP
Lettuce	South Zone except for France	Indoxacarb 150 g/L EC (DPX-KN128 150 g/L EC)	F	*Autographa gamma* *Chrysodeixis chalcites* *Helicoverpa armigera* *Mythimna unipuncta* *Spodoptera exigua* *Spodoptera littoralis*	EC	150	hydraulic ground directed boom	BBCH 13-49 Seed crops BBCH 13-59	a) 4 b) 4	7 days	a) 250 b) 1000	200-1000	a) 37.5 b) 150	1	

* For uses where the column „Remarks“ in marked in grey further consideration is necessary. Uses should be crossed out when the notifier no longer supports this use(s).

(a) For crops, the EU and Codex classification (both) should be taken into account ; where relevant, the use situation should be described (e.g. fumigation of a structure)

(b) Outdoor or field use (F), greenhouse application (G) or indoor application (I)

(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds

(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)

(i) g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxypyr). In certain cases, where only one variant synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).

(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application

(k) Indicate the minimum and maximum number of application possible under practical conditions of use

(e) GCPF Codes – GIFAP Technical Monograph N 2, 1989
(f) All abbreviations used must be explained
(g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plant – type of equipment used must be indicated
(l) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha
(m) PHI - minimum pre-harvest interval

1.5.2. Further information on representative uses

For the representative uses please refer to table above, in 1.5.1. Details of representative uses.

The representative crops, lettuce, maize (grain and silage), and sweet corn, are treated with tractor-mounted hydraulic field sprayers with ground-directed booms. For maize (grain and silage) and sweet corn the application must be made from above the crop.

There are no expected adverse effects on the representative crops. In addition, the product is an insecticide and has been in use for several years. Effects on succeeding crops are not considered to be an issue.

1.5.3. Details of other uses applied for to support the setting of MRLs for uses beyond the representative uses

Not applicable

1.5.4. Overview on authorisations in EU Member States

Authorisations for a range of different formulations have been achieved in Europe. These include different formulation types (EC and WG). The complete list of currently registered uses can be found in the supplementary dossier, document D-2.

Level 2

INDOXACARB

2. SUMMARY OF ACTIVE SUBSTANCE HAZARD AND OF PRODUCT RISK ASSESSMENT

Summary of methodology proposed by the applicant for literature review and for all sections

A literature review was carried out for Indoxacarb according to the requirements of the Regulation (EU) No 844/2012 (the AIR3 renewal regulation), which itself refers to Article 8(5) of Regulation (EC) No 1107/2009. The review itself is in accordance with the EFSA Guidance document as published in EFSA Journal 2011; 9(2):2092.

The key question is whether any scientific peer-reviewed open literature published within the last ten years before the date of submission of the dossier would be relevant for the risk assessment of Indoxacarb and relevant metabolites in the context of side-effects on health, the environment and non-target species. Wherever such relevance could not be excluded, the scientific findings need to be discussed in detail in the submission for Renewal of Approval and, if necessary, the risk assessments would be updated accordingly.

Relevance criteria

The table below lists the selection criteria applied to the results of the search for peer reviewed open literature relevant to indoxacarb and relevant metabolites. Relevant metabolites of a particular active substance as defined by Regulation (EC) No 1107/2009 can only be definitively identified at the end of a risk assessment. Scientific literature search will focus on metabolites, degradation products, or transformation products of an active substance formed either in the organism or in the environment.

Data requirement(s) (indicated by the correspondent data point number(s) as identified in Commission Regulation (EU) 283/2013)	Criteria for relevance
All Data Points	1. The dose levels or application rates reflect the proposed GAP.
	2. The test system, target crop, or species are prescribed by Regulation (EC) No 1107/2009 or the relevance is explained if not standard.
	3. Well identified test material, including its purity and impurity profile, is described.
	4. Study design and/or execution are consistent with relevant study guidelines.
	5. The endpoint is relevant to an EU data point as prescribed by Regulations (EU) No 283/2013 and 284/2013
Toxicological and toxicokinetic studies	6. Description of the observations, examinations, analysis performed, or necropsy are well described.
	7. The conditions of exposure should be from a legally registered use of the product.
Residues in or on treated products, food and feed (metabolism and residues data)	8. The application method(s) complies with Good Agriculture Practice (GAP)
	9. Appropriate in-life/processing conditions are used and/or are well described
Fate and behaviour in the environment	10. The model is appropriate for European regulatory requirements.
	11. The input parameter selection is appropriate based on European regulatory requirements.
	12. The pedoclimatic conditions are appropriate.
Ecotoxicological studies	13. A relevant route of exposure is presented.

Search criteria

Reasonable effort was taken to locate all sources of relevant peer reviewed open literature concentrated on comprehensive databases containing worldwide coverage of biology, chemistry, biomedical, agricultural and environmental fields. The search ranged up to 10 years and within 6 months of the submission date (30/04/2015). The initial search is a single concept search capturing all data points using search terms and synonyms for the active substance. If a large number of search results are returned from the single concept search making assessment for relevance impractical, a separate, focussed search is conducted for grouped data points. A separate single concept search is also conducted for each relevant metabolite.

Relevant study selection-results of the selection process

Obviously non-relevant studies in open literature search were excluded by applying the relevance criteria previously defined in Table above. A total of 1082 summary records were reviewed; of these 1076 were not relevant. When the summary records did not contain sufficient information to assess relevance, full text documents were reviewed in detail for relevance according to the previously defined criteria. After reviewing full text documents of potentially relevant studies, 56 were excluded from further consideration. Relevant studies and studies of unclear relevance 6 have been selected for inclusion in the dossier.

The tables below summarise the results of the selection process including the number of summary records and full text documents assessed.

Literature search results: Mammalian toxicology

Data requirement(s) captured in the search	Number
Total number of summary records retrieved after all searches of peer-reviewed literature (excluding duplicates)	248
Number of summary records excluded from the search results after rapid assessment for relevance	232
Total number of full-text documents assessed in detail	16
Number of studies excluded from further consideration after detailed assessment for relevance	9
Number of studies not excluded for relevance after detailed assessment (*i.e.*, relevant studies and studies of unclear relevance)	7

Literature search results: Metabolism and Residue

Data requirement(s) captured in the search	Number
Total number of summary records retrieved after all searches of peer-reviewed literature (excluding duplicates)	452
Number of summary records excluded from the search results after rapid assessment for relevance	452
Total number of full-text documents assessed in detail	0
Number of studies excluded from further consideration after detailed assessment for relevance	0
Number of studies not excluded for relevance after detailed assessment (*i.e.*, relevant studies and studies of unclear relevance)	0

Literature search results: Environmental Fate

Data requirement(s) captured in the search	Number
Total number of summary records retrieved after all searches of peer-reviewed literature (excluding duplicates)	64
Number of summary records excluded from the search results after rapid assessment for relevance	64
Total number of full-text documents assessed in detail	0
Number of studies excluded from further consideration after detailed assessment for relevance	0
Number of studies not excluded for relevance after detailed assessment (*i.e.*, relevant studies and studies of unclear relevance)	0

Literature search results: Ecotoxicology

Data requirement(s) captured in the search	Number
Total number of summary records retrieved after all searches of peer-reviewed literature (excluding duplicates)	314
Number of summary records excluded from the search results after rapid assessment for relevance	267
Total number of full-text documents assessed in detail	47
Number of studies excluded from further consideration after detailed assessment for relevance	46
Number of studies not excluded for relevance after detailed assessment (*i.e.*, relevant studies and studies of unclear relevance)	1

The outcomes of the review of scientific open literature and these scientific papers are discussed by the RMS in Volumes 3 of the RAR for each section.

2.1. IDENTITY

All relevant points relating to identity of active substance and plant protection product have been addressed in Volumes 3 B1 and volume 4.

2.2. PHYSICAL AND CHEMICAL PROPERTIES

No literature search has been performed for physico-chemical properties.

2.2.1. Summary of physical and chemical properties of the active substance

The pure active substance of indoxacarb (DPX-KN128) is a white crystalline powdered solid that melts at 88.1°C. Indoxacarb has no evident pKa, and it would not be expected to dissociate at relevant environmental pHs. The aqueous solubility of indoxacarb (DPX-KN128) is approximately 0.20 ppm at 25°C. The vapour pressure (2.5×10^{-8} Pa at 25°C) and the Henry's Law Constant (6.0×10^{-10} atmosphere m^3/mole at 25°C) indicate that volatilisation is not a significant route of dissipation for indoxacarb. There should be no safety concerns regarding explosivity, flammability, self-ignition, or oxidising properties based on the tests. Since the CLP tests became effective for substances and there was no correspondence between tests, **studies tests should be performed according to CLP criteria (manual UN RTDG)**

2.2.2. Summary of physical and chemical properties of the plant protection product

The formulation Indoxacarb 150 g/L EC is an Emulsifiable Concentrate. All studies have been performed in accordance with the current requirements and the results are deemed to be acceptable. The appearance of the product is that of straw yellow to brown, with pungent sweet pear odour. It is not explosive and has no oxidizing properties. The product is not fammable and has a flash point of 69 ± 3°C. It has a self-ignition temperature of 255±5°C. Since the CLP tests became effective for plant production products and there was no correspondence between tests, **studies should be performed according to CLP criteria (manual UN RTDG).**
In aqueous solution (1%), it has a pH value between 5.0 and 5.4 at 25°C. There is no effect of low and high temperature on the stability of the formulation, since after 7 days at 0°C and 14 days at 54°C, neither the active ingredient content nor the technical properties were changed. The stability data indicate a shelf life of at least 2 years at ambient temperature when stored in fluorinated High Density Polyethylene (HDPE/F) and Polyethylene/Ethyl Vinyl Alcohol (PE/EVOH). However, **relevant impurities content in the formulation should be determined before and after storage study or a**

justification for "non-formation" of these impurities during the formulation or the storage is required. Its technical characteristics are acceptable for Emulsifiable Concentrate formulation.

The formulation is not classified for the physical-chemical aspect.

2.3. DATA ON APPLICATION AND EFFICACY

2.3.1. Summary of effectiveness

More detailed consideration will be fully assessed in the context of subsequent applications for products authorization.

2.3.2. Summary of information on the development of resistance

Possible occurrence of resistance: Indoxacarb (DPX-KN128) acts as "voltage-dependant sodium channel blocker" according to the IRAC International Mode of Action classification, also coded as MoA group 22. Indoxacarb is the only member of the MoA subgroup 22 A and belongs to the oxadiazine chemical class. It has to be noted that metaflumizone also belongs to MoA group 22, but to the subgroup 22 B. The pyrethroids, which also act on the neuronal sodium channel, act on a different "gate" which has the effect of stopping the sodium channel from closing. This is the opposite of the mechanism of indoxacarb (=DPX-MP128).

The Insecticide Resistance Action Committee (IRAC) continuously monitors globally for cases of resistance and according to the database, some cases of resistance have been noted in the literature.

Cases of indoxacarb resistance indicated on the IRAC database for agricultural pests – February 2016 (http://www.pesticideresistance.org/search.php)

Genus Species	**Common Name(s)**	**Cases**
Choristoneura rosaceana	oblique banded leafroller	4
Earias vittella	the spotted bollworm	5
Helicoverpa armigera	cotton bollworm	6
Heliothis virescens	tobacco budworm	2
Lobesia botrana	european grapevine moth	1
Plutella xylostella	diamond-back moth	49
Sitophilus zeamais	maize weevil, rice weevil	7
Spodoptera exigua	beet army worm, lesser army worm	38
Spodoptera litura	mediterranean climbing cutworm	34
Tuta absoluta	tomato leafminer	3

Preventive actions are proposed. Indeed, repeated and exclusive use of indoxacarb may lead to the build-up of resistant strains of insects in some crops. Some insect species are known for their propensity to develop resistance to products used repeatedly for control. Since the development of resistance cannot be predicted, this product should be used as part of the resistance management strategies established for the use area (IRM programmes). These strategies should include incorporation of cultural and biological control practices, alternation of the mode-of-action (MoA) group of insecticides on succeeding generations and targeting the most susceptible life stage.

A set of management strategies to reduce the risk of developing resistance are proposed. Modifiers applied to the use of the active substance and its products include the restriction on the maximum number of applications, minimum rate per application and primarily the alternation with different modes of action. It is considered that with these modifiers in place, the risk is reduced to a sustainable level.

Susceptibility monitoring methods for indoxacarb: Currently a wide range of bioassay and biochemical tests are employed to characterise the susceptibility of target pests to insecticides. There are currently several approved IRAC methods covering a wide range of pest species which can be found on the IRAC website and can apply to indoxacarb too. In the time period from 2002 to 2013, numerous field populations of *H. armigera, S. exigua, S. littoralis, P. xylostella, O. brumata, A. orana, C. pomonella, L. botrana, E. ambiguella, Tuta absoluta,* and *Meligethes aeneus* were tested in Europe for establishing their sensitivity to indoxacarb before and soon after commercial introduction (baseline monitoring). After the screening and validation of different laboratory assay methods, also a user-friendly kit (LFB) was optimized and adopted for extended semi-field sensitivity screening.

Management strategy: Indoxacarb is providing to growers a valuable resistance management option for insect pest control; however it is considered that the unrestricted use of indoxacarb would pose a significant resistance risk. It's therefore indicated that below measures are adopted in order to reduce the potential risk connected to unrestricted use.

Indoxacarb should always be applied within spray programs involving the use of other effective insecticides with a different mode of action. Two consecutive pest generations should not be exposed to the same insecticidal MoA. Insecticide MoA alternation is the primary route to resistance avoidance.

2.3.3. Summary of adverse effects on treated crops

More detailed consideration will be fully assessed in the context of subsequent applications for products authorization.

2.3.4. Summary of observations on other undesirable or unintended side-effects

More detailed consideration will be fully assessed in the context of subsequent applications for products authorization.

2.4. FURTHER INFORMATION

2.4.1. Summary of methods and precautions concerning handling, storage, transport or fire

Hazards identification:

On the basis of available information indoxacarb (DPX-KN128) is not expected to produce any significant adverse health or environmental effects when the recommended use instructions are followed.

Fire Fighting Measures:

Flash Point:	NA
Hazardous Products of Combustion:	None known. In the event of fire, the formation of hydrogen cyanide, carbon monoxide, nitrogen oxides, and sulphur oxides must be anticipated. Not subject to the Regulation on Flammable Liquids (VbF).
Extinguishing Media:	In case of fire, use water (flood with water), dry chemical, CO_2, or alcohol foam. Fire-fighting water must be contained and treated.
Unusual fire and Explosion Hazards:	None
Fire Fighting Equipment:	Fire fighters and others exposed to products of combustion should wear self-contained breathing apparatus. Equipment should be thoroughly decontaminated after use.

Transport:

Toxic solid, organic, n.o.s. (indoxacarb), 6.1, UN 2811, PG III

Transport: **ADR**

Class:	6.1
Packaging group:	III
UN-No.:	2811
Proper shipping name:	Toxic solid, organic, n.o.s. (indoxacarb)
Tunnel restriction code	(E)
IATA_C	
Class:	6.1
Packaging group:	III
UN-No.:	2811
Proper shipping name:	Toxic solid, organic, n.o.s. (indoxacarb)
Special precautions for user:	DuPont internal recommendations and transport guidance: ICAO/IATA cargo aircraft only

IMDG

Class:	6.1
Packaging group:	III
UN-No.:	2811
Proper shipping name:	Toxic solid, organic, n.o.s. (indoxacarb)
Marine pollutant:	Marine pollutant

2.4.2. Summary of procedures for destruction or decontamination

A specific study on the thermal decomposition has not been carried out. Current practice is to incinerate at a temperature greater than 900°C with a residence time of 2-4 sec in the chamber. Oxygen supply should be adjusted to generate <100 ppm carbon monoxide in the stack.

The recommended means of safe disposal is by controlled incineration at an approved chemical waste facility. This is a standard process and no further detailed instructions are required.

Package product wastes: Waste should be disposed of in accordance with local and national regulations. Packaging should be incinerated at a suitable, licensed plant. The product should not be allowed to enter drains, water courses or the soil.

2.4.3. Summary of emergency measures in case of an accident

Indoxacarb (DPX-KN128) technical is not produced or formulated in the EU so accidental release of the technical material is not likely to occur in the EU. However, if small sample quantities accidentally are released to the environment the clean-up procedure listed in the material safety data sheet should be followed.

2.5. METHODS OF ANALYSIS

2.5.1. Methods used for the generation of pre-authorisation data

Methods used for the generation of pre-authorisation were evaluated in Volume 3.B.5.

2.5.2. Methods for post control and monitoring purposes

Analytical methods for the determination of active substance and relevant impurities in the active substance as manufactured and in plant production product:

Analytical methods for the determination of active substance and relevant impurities in the active substance are available and validated.
Analytical method for the determination of active substance in formulation was available. Nevertheless, analytical method for the assay of indoxacarb in formulation product should be able to determine each isomer in the presence of the other one. A direct determination of the active S-isomer Indoxacarb (DPX-KN128) in the plant production product is particularly important for control of formulation. Therefore, **a full validation of a specific method for DPX-KN128 should be provided.**
Analytical methods for the determination of relevant impurities in the formulation were available. However, LOQ were higher than calculated/expected value for relevant impurities in formulated Indoxacarb 150 g/L EC. **Methods with lower LOQ are required for product stage.**

Analytical methods for residue determination in food of plant origin:

An analytical method (Čermák, J., 2013) and its ILV (Stanislowski, T., 2015) based on LC-MS/MS for the determination of indoxacarb residue in crops has been provided and validated with a LOQ of 0.01mg/kg in high water content, acidic, fatty and dry commodities. As data have been provided for two mass transitions, the method is considered as highly specific.

However a data gap was identified in the RAR concerning Extraction efficiency. Justification given by notifier for Extraction Efficiency, based on "similar" physical or chemical properties (e.g. density, dipole moment, dielectric constant, "polarity") of the different solvents is not sufficient. Thus, extraction efficiency in different solvent systems used in monitoring studies (acetone/water for high water content, acidic and dry commodities and acetone/acetonitrile for high fat content crops) should be provided.

Analytical methods for residue determination in food of animal origin:

An analytical method (J.J Stry, 2004, report DuPont 12739 Rev1) for the determination of indoxacarb residue in animal products by LC-MS/MS has been provided and is validated with a LOQ of 0.01mg/kg for indoxacarb (sum of isomers) and metabolites IN-JU873, IN-JT333, IN-KB687, IN-

KG433 and IN-KT319 in liver, muscle, fat, skin, whole eggs, egg white, egg yolks. For eggs, ion ratio data are acceptable for each analyte, so the method can be considered highly specific. **For other matrix, the method is not highly specific** since confirmatory data were not provided. **Additionally, the Extraction efficiency was not presented**.

No validation data were presented for milk matrix.

An ILV (P. Connolly, 2004, report DuPont 13651 Rev1) of method J.J Stry, 2004 (report DuPont 12739 Rev1) for the determination of indoxacarb residue in foodstuff of animal origin has been provided but is not validated. **The number of samples per level used for accuracy/precision is not sufficient.**

An analytical method (S. Richter, 2013) based on DFG S19 multiresidue method using LC-MS/MS for the determination of indoxacarb residue in foodstuff of animal origin (milk, eggs, liver and muscle) has been validated with a LOQ of 0.01mg/kg. **Notifier should provide the extraction efficiency in different solvent systems used in monitoring studies. No validation data was presented for fat matrix. Additionally, no ILV was provided.**

DFG multiresidue method S19 (Linkerhagner, M., Guinivan, R.A., 2001 And Class, T (2001), DuPont-2338, Revision No. 1 and DuPont-6224) was validated for indoxacarb (sum of isomers) and IN-JT333 in animal product (milk, eggs, meat, liver, fat, and kidney) in the previous DAR. **However, according to actual guidance method is not considered as fully validate as linearity and specificity of main method were missing. Additionally, study reports were not presented and specificity is missing. It's ILV (Class, T. 2000, DuPont-39006) have been provided for two columns of different polarity, the method can be considered as highly specific.**

Analytical methods for residue determination in soil:

The analytical method (DuPont-35025) for the determination of indoxacarb residues in soil is considered as validated with an LOQ of 0.001 mg/kg for indoxacarb and its metabolites (IN-MK643, IN-MK638, IN-KB687, IN-KG433, IN-JU873, IN-KT413, IN JT333).

Analytical methods for residue determination in water:

Method (DuPont-9605) is considered as validated for determination of Indoxacarb, IN-KT413, IN-MS775, IN-JT333, IN-MP819, IN-JU873 and INKG433 with an LOQ of 0.05µg/kg in ground water, drinking water and surface water.

Analytical methods for residue determination in air:
The analytical method (DuPont-18596) for the determination of indoxacarb residues in air is considered as validated with an LOQ of 0.10 $\mu g/m^3$.

Analytical methods for residue determination in body fluids and tissues:

The analytical method (DuPont-24760) for the determination of indoxacarb residues in plasma is considered as validated with an LOQ of 0.0020 mg/. **Nevertheless, the method is not considered as highly specific, a confirmatory method is required.**

2.6. EFFECTS ON HUMAN AND ANIMAL HEALTH

DPX-KN128 is the insecticidally active, S-enantiomer of a compound belonging to the novel oxadiazine class of insecticides. The R-enantiomer, IN-KN127, is not insecticidally active. DPX-MP062 (75:25) and DPX-JW062 (50:50) are enantiomer blends of DPX-KN128 and IN-KN127. DPX-MP062 contains the respective isomers in a ratio of approximately 75:25, while DPX-JW062 is a racemic (50:50) mixture. Development of the oxadiazine class of insecticides began with DPX-JW062 (50:50). Processes were subsequently developed that allowed for commercial production of DPX-MP062 (75:25), whose enhanced ratio of the insecticidally active enantiomer allowed for lower use rates of the end-use product and thus lower environmental and dietary exposures. Process breakthroughs in 2005 allowed for the commercial production of >99% indoxacarb (DPX-KN128) technical containing ≤1% IN-KN127. Today, DPX-KN128 is the primary technical material used as basis for formulation of end-user products. Although DPX-MP062 technical (75:25) was considered the reference material used as basis for the EU approval of the indoxacarb in 2006, DPX-KN128 (99:1) is the active substance intended to be approved in the context of the renewal of indoxacarb.

The concentration of the insecticide active isomer DPX-KN128 and the insecticide inactive isomer IN-KN127 are shown for the 3 forms of technical active materials in the table below:

Test Substance	**Percent DPX-KN128**	**Percent IN-KN127**
DPX-JW062	50	50
DPX-MP062	75	25
DPX-KN128	>99	<1

For better clarity, the compounds will be called DPX-JW062 (50:50), DPX-MP062 (75:25) and DPX-KN128 (99:1) in the RAR.

A full battery of toxicity and metabolism studies was conducted with DPX-JW062 (50:50). Metabolism, acute toxicity, genotoxicity, rat developmental toxicity, neurotoxicity, and targeted repeated dose toxicity studies were conducted with DPX-MP062 (75:25) to demonstrate equivalence with DPX-JW062 (50:50).
Targeted toxicity studies in the most sensitive species and gender were conducted with DPX-KN128 (99:1) to demonstrate equivalence to DPX-JW062 (50:50) and DPX-MP062 (75:25). Since DPX-KN128 was present at 50-75% in the toxicity studies conducted with DPX-JW062 and DPX-MP062, these studies can be used to support the toxicity database for indoxacarb and are relied on where specific studies with DPX-KN128 technical have not been conducted. Additionally, as shown from the results of the three 90-day toxicity studies performed either on DPX-JW062, DPX-MP062 or DPX-KN128, the toxicity of the three compounds seem to be quite similar and no further toxicity testing was considered needed.

The table below illustrates the studies performed on the different technical active materials tested.

Table 2.6-1
Indoxacarb studies

Study Type	DPX-JW062 (50:50)	DPX-MP062 (75:25)	DPX-KN128 (99:1)
Rat metabolism	X	X	-
Acute oral/dermal LD_{50}	-	X	X
Acute inhalation LC_{50}	X	-	-
Skin sensitization, skin/eye irritation	-	X	X
Phototoxicity	-	-	X
Genotoxicity battery	-	X	X
28-day oral (rats/mice)	X	-	-
28-day dermal	-	X	-
90-day oral (rats)	X	X	X
90-day oral (mice)	X	-	-
90-day oral (dogs)	X	-	-
1-year oral (dogs)	X	-	-
2-year oral (rats)	X	-	-
18-month oral (mice)	X	-	-
Multigeneration reproduction	X	-	-
Rabbit developmental	X	-	-
Rat developmental	X	X	X
Acute oral neurotoxicity (rats)	-	X	-
Subchronic oral neurotoxicity (rats)	-	X	-
Rat developmental neurotoxicity	-	-	X
Immunotoxicity	-	-	X

Test substance specification can be determined from the test substance code which is a research and development code number given to a specific batch of produced material (either technical or formulated). The approximate composition of the material(s) used in the various tests is given in the following tables.

Table 2.6-2
Active substance specification

Test substance code	Description	Purity (%)[a]	Ratio of Isomers
DPX-JW062-34	DPX-JW062 Technical	94.7	50% DPX-KN128 50% IN-KN127
DPX-JW062-69	DPX-KN128 techncial	90.95	90.4% DPX-KN128 0.55% IN-KN127
DPX-JW062-106	DPX-JW062 technical	95	47% DPX-KN128 47% IN-KN127
DPX-JW062-112	DPX-JW062 technical	94.7	50% DPX-KN128 50% IN-KN127
DPX-KN128-31	DPX-KN128 technical	99.7	99.7% DPX-KN128 IN-KN127 not detected
DPX-KN128-098	DPX-KN128 technical	95.5	95.5% DPX-KN128 <0.01% IN-KN127
DPX-KN128-215	DPX-KN128 technical	98.4	98.4% DPX-KN128 IN-KN127 not detected
DPX-KN128-424	DPX-KN128 technical	99.06	99.06% DPX-KN128 <0.1% IN-KN127
DPX-MP062-51	DPX-MP062 technical	94.5	75% DPX-KN128 25% IN-KN127
DPX-MP062-51A	DPX-MP062 technical	94.5	75% DPX-KN128 25% IN-KN127
DPX-MP062-51B	DPX-MP062 techncial	94.5	75% DPX-KN128 25% IN-KN127
DPX-MP062-216	DPX-MP062 technical	95.8	72.3% DPX-KN128 23.5% IN-KN127
DPX-MP062 21793-02	DPX-MP062 technical	94.5	75% DPX-KN128 25% IN-KN127

[a] Purity refers to the weight percent of the sum of DPX-KN128 + IN-KN127.

Table 2.6-3
Metabolite specification

Test substance code	Description	Purity (%)
JT333-1	IN-JT333 technical metabolite	>95%
JT333-20	IN-JT333 technical metabolite	98.7%
KG433-3	IN-KG433 technical metabolite	98%

Classification and labelling:

A harmonised classification and labelling for indoxacarb was adopted by the ECHA Committee for Risk Assessment (RAC) in June 2011. The resulting classification is available in Commission Regulation (EU) No 944/2013 (5th adaptation to technical and scientific progress of Regulation (EC) No 1272/2008) and the classification for human health is the following:

Acute Tox 3 H301
Acute Tox 4 H332
STOT RE 1 H372 (blood, nervous system, heart)
Skin Sens 1B H317

This classification was considered relevant for indoxacarb DPX-KN128 (99:1) (CAS: 173584-44-6) and for the enantiomeric reaction mass 75:25 S:R (CAS: 144171-61-9).

The toxicological studies available in the CLH report are the same as those evaluated in the first DAR of indoxacarb. Therefore, the majority of studies performed on DPX-KN128 (99:1) and submitted for

the purpose of this renewal were not included in the CLH report and were not assessed by the ECHA RAC. Nevertheless, the RMS considers that the newly submitted studies do not change the classification adopted by ECHA RAC.

2.6.1. Summary of absorption, distribution and excretion in mammals

ADME studies were carried out in rats using DPX-JW062 (a racemic (50:50) mixture of DPX-KN128 and IN-KN127; trifluoromethoxy- and indanone-labels) and DPX-MP062 (a 75:25 mixture of DPX-KN128 and IN-KN127; indanone-label).

Absorption
Upon low dose (5 mg/kg bw) oral administration of DPX-JW062 (50:50) absorption was rather slow and at least 64% of the administered dose for both sexes (trifluoromethoxyphenyl-label). This is based on the sum of urinary excretion and radioactivity levels in tissues by 168 h after administration.
In a separate experiment, absorption defined as the sum of the 48-h urinary and biliary excretion resulted in absorption values of at least 62% for males and at least 44% for females after administration of DPX-JW062 (50:50). However, because of the slow excretion (used to define absorption), the 48-hr observation is considered less relevant. Furthermore, carcass residues were not measured in the bile duct cannulated rats.
Saturation of absorption (less than 11%) occurred at high dose administration (150 mg/kg).

The results of the study with indanone-radiolabelled DPX-MP062 (75:25) (5 mg/kg bw, single dose only) were almost comparable to those obtained from rats dosed with indanone-radiolabelled DPX-JW062 (50:50). One apparent difference was the higher absorption in females of DPX-MP062 (75:25) (58%) compared with DPX-JW062 (50:50) (45%) based on sum of urinary excretion and tissue levels at 168 h in the rats that were administered indanone-labelled test substances.
Absorption was not measured with trifluoromethoxyphenyl-radiolabelled DPX-MP062 (75:25). Since with DPX-JW062 (50:50), absorption with trifluoromethoxyphenyl-labelled test substance was higher than with indanone-labelled test substance, it cannot be excluded that actual absorption of DPX-MP062 (75:25) was higher than 58%. However, since this was not studied, the minimal absorption of DPX-MP062 (75:25) was concluded to be 58% (worst-case assumption) and overall, the agreed oral absorption used in the context of the first inclusion of indoxacarb was 60%.

Repeated low dose administration of trifluoromethoxyphenyl-labelled DPX-JW062 (50:50) to female rats did not appear to influence the absorption observed upon a single dose administration, based on comparison of urinary excretion levels.

Excretion
Excretion of radiolabel was rather slow. By seven days after a single dose (5 mg/kg) of indanone-radiolabelled DPX-JW062 (50:50), excretion of the radiolabel in urine was 37 and 41% for females and males, respectively and in faeces 44% both for females and males. For the trifluoromethoxyphenyl-labelled DPX-JW062 (50:50), these values were somewhat different, due to cleavage of the main structure of the parent compound during biotransformation, i.e. in urine 47 and 55% and in faeces 27 and 30% for females and males, respectively.

Excretion of radiolabel in rats that were administered DPX-MP062 (75:25) (indanone-labelled) was 45 and 35% in urine and 33 and 47% via faeces in female and male rats, respectively. This reflects the higher absorption in females for DPX-MP062 (75:25) compared to DPX-JW062 (50:50).

Distribution
By 168 h after a single oral dose administration of indanone-labelled DPX-JW062 (50:50) the total tissue content of radiolabel was 7.8 and 3.4% for females and males, respectively. Upon administration of the trifluoromethoxyphenyl-labelled DPX-JW062 (50:50), these values were higher, i.e. 17 and 10%, respectively.

By 168 h after a single oral dose administration of DPX-MP062 (75:25) (indanone labelled) the tissue levels were 13 and 4.4% for females and males, respectively. This indicates sex-specific distribution, especially for DPX-MP062 (75:25).

Most of the radiolabel of administered DPX-JW062 (50:50) and DPX-MP062 (75:25) was distributed to fat and blood. Importantly, in comparison with administration of radiolabelled DPX-JW062 (50:50), a greater amount of the radiolabelled DPX MP062 dose appeared to be retained by tissues, particularly fat. Furthermore, for both test substances, the decline of radiolabel was significantly lower in fat compared to plasma. Remarkably, the radioactivity levels in red blood cells upon administration of [trifluoromethoxyphenyl(U)-^{14}C]DPX-JW062 but not [indanone-1-^{14}C]DPX-JW062 (50:50) were much higher than the levels in plasma apparently due to retention in red blood cells of radioactivity associated with the trifluoromethoxyphenyl portion of the molecule. The latter hypothesis was supported by an additional RBC distribution study with radiolabelled DPX-JW062 (50:50), in which the trifluoromethoxyaniline metabolite P0036 was shown to be exclusively associated with RBCs.

The retention and elimination of the metabolite IN-JT333 from fat and the binding of some component to red blood cells appeared to be the overall rate determining processes for elimination of radioactivity from the body.

Upon repeated dose administration of trifluoromethoxyphenyl labelled DPX-JW062 (50:50) (5 mg/kg) to rats (studied only in female rats), an increase in tissue radioactivity levels was observed for up to 8 days. The relative amount of radiolabel retained in tissues of rats was smaller (8.4% of the total administered radiolabel) than after a single dose administration (17%). In addition, in fat and red blood cells the ratio of the level of radiolabel seven days after the last of multiple dose administration compared to seven days after a single dose, amounted up to a factor 10 and 100, respectively.

Metabolism

DPX-JW062 (50:50) and DPX-MP062 (75:25) were extensively metabolised, based on very low excretion of parent compound in bile (determined for DPX-JW062 (50:50) only) together with extensive excretion of metabolised dose in urine and faeces. Both for DPX-JW062 (50:50) and DPX-MP062 (75:25) some parent compound remained unabsorbed and was excreted in faeces. In urine, no parent compound was observed.

Biotransformation started with either enzymatic removal of the methoxycarbonyl group leading to JT333 (KN125/KN124) or hydroxylation at the benzylic position in the indanone moiety leading to 5-OH-JW062. Both metabolites were found in fat and faeces. For the first reaction, gender specificity and substrate stereospecificity was observed as in females the formation of IN-JT333 was the most important biotransformation step. Furthermore, the S-isomer (KN128) of DPX-JW062 (50:50) was the preferred substrate in this reaction, leading to an increased formation of IN-KN125 over IN-KN124. In male rats, formation of 5-OH-JW062 (sum of two enantiomers) was more important than the formation of IN-JT333 (sum of two enantiomers). Further steps in the extensive biotransformation are indicated in the proposed metabolic pathway as presented in the following section.

***In vitro* and *in vivo* rat microsomal metabolism**

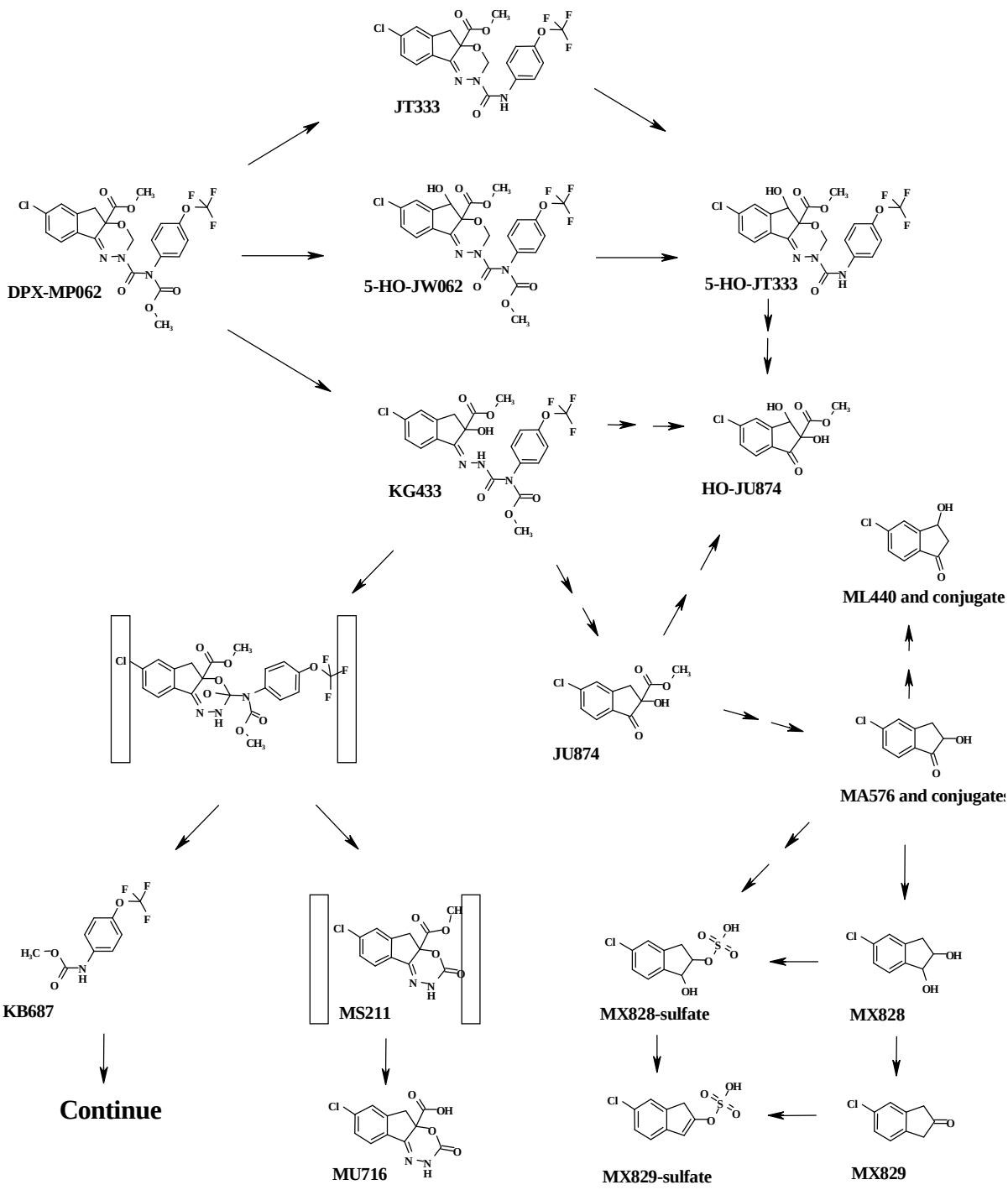
Microsomes from both sexes showed a decline in the concentration of DPX-JW062 (50:50). The rate of decline in male rat microsomal suspensions ($t_{1/2}$ = 25.5 min) was faster than in female suspensions ($t_{1/2}$ = 67.6 min). The corresponding area-under-the-curve (AUC) (nmol × min/ml) for male rat microsomes was 137.8 compared with 500.6 for female rat liver microsomes. These values were used to estimate intrinsic hepatic clearance. The range of estimates for intrinsic hepatic clearance (mL/min/kg body weight) of DPX-JW062 (50:50) in the male rat (26.2 to 35.0 mL/min/kg body weight) were approximately 2.2 to 3.0 times faster than in female rats (11.6 to 11.9 mL/min/kg body weight).

Overall
The toxicokinetics and overall metabolism of DPX-MP062 (indanone radiolabelled) was qualitatively similar to that observed for the corresponding indanone radiolabelled DPX-JW062. However, quantitative differences occurred, especially for total radioactivity observed in fat (greater for DPX-MP062 (75:25)). Furthermore, based on the available data, DPX-MP062 (75:25) seems to be more absorbed in female rats than DPX-JW062 (50:50). Important gender- and stereospecific biotransformation was observed which was more pronounced for DPX-MP062 (75:25) as it contains an enantiomeric excess of the S-enantiomer. It appeared that the S-isomer KN128 is preferred as a substrate for the enzymatic removal of the N-carboxymethyl group in the parent compound leading to IN-JT333, especially in female rats. In male rats an increased (relative to females) formation of 5-HO-JW062 was observed.

DPX-KN128 (99:1)
No ADME study was available with the pure S-enantiomer DPX-KN128. ADME profiles of the racemic DPX-JW062 (50:50) and the enantiomer blend DPX-MP062 (75:25) containing DPX-KN128 and IN-KN127 in a ratio of approximately 75:25 were available and were qualitatively similar. Nevertheless, compared to DPX-JW062 (50:50), administration of DPX-MP062 (75:25) resulted in a higher absorption in female rats and a greater retention of radioactivity in tissues, particularly in fat. DPX-KN128 was shown to be the preferred substrate for the enzymatic removal of the N-carboxymethyl group in the parent compound, leading to the formation of the metabolite IN-JT333.
It can thus be expected that administration of pure DPX-KN128 (99:1) to rats would increase the differences observed between the racemic DPX-JW062 (50:50) and the enantiomeric mixture 75:25 DPX-MP062.
Based on these data, it is considered appropriate to use the oral absorption set for DPX-MP062 in the context of the first inclusion of indoxacarb (75:25), i.e. 60%.

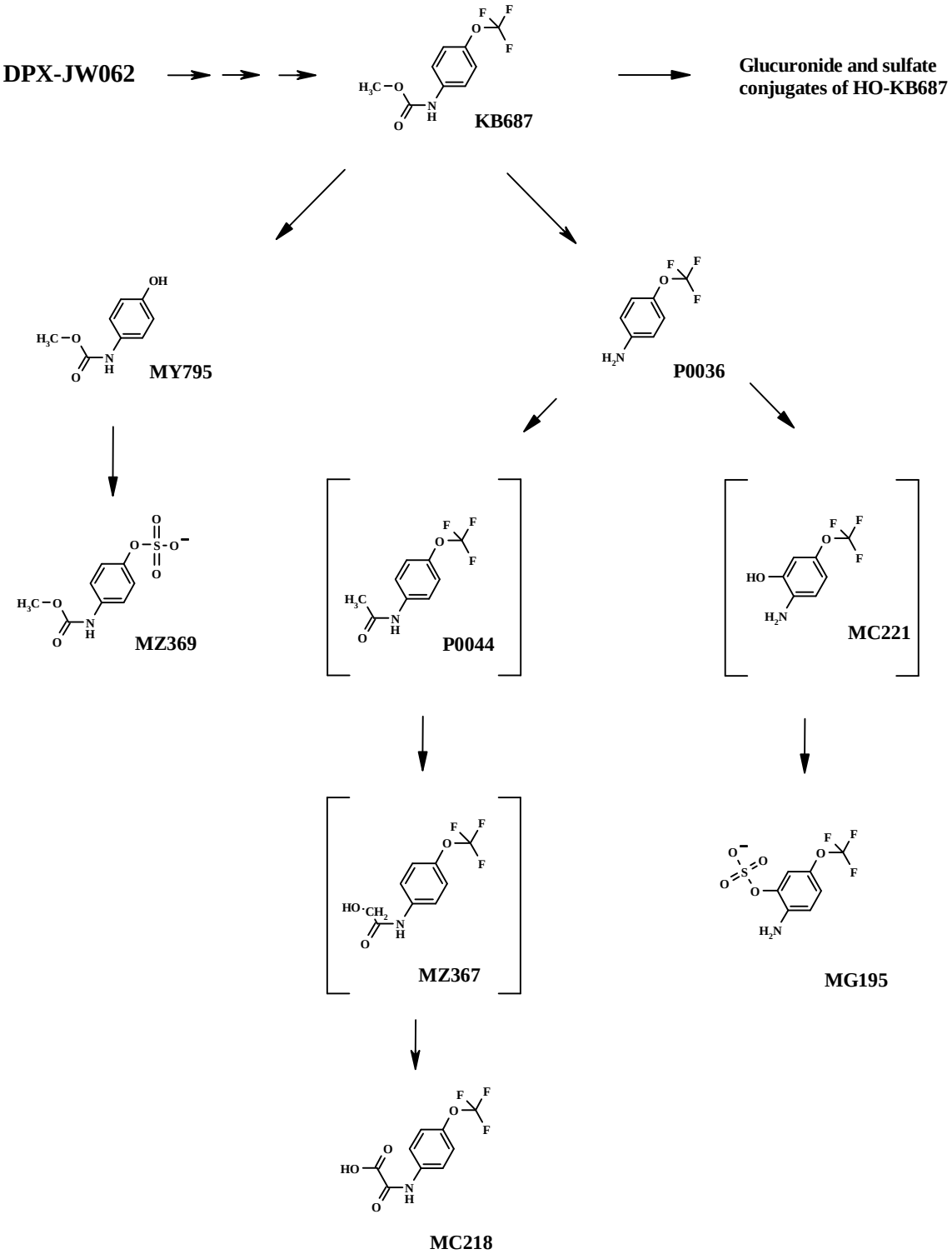
According to co-RMS (ES): "*Available data only allow to establish absorption at 60% as worst case assumption. After 168 h absorption in females, based on excretion in urine and tissues is higher for DPX-MP062 (58%) than for DPX-JW062 (45%). A metabolism study with DPX-KN128 would be therefore very convenient*."

Figure 2.6.1-1
Proposed metabolic pathway of DPX-MP062 in the rat



[ ] **Proposed intermediates**

Figure 2.6.1-1
Proposed metabolic pathway of DPX-MP062 in the rat (continued)



[ ] Proposed intermediates

Comparative *in vitro* metabolism study:

A comparative *in vitro* metabolism study using human and animal materials is required according to Regulation (EU) No 283/2013. No study was provided by the applicant. The following justification was submitted:

"This study was not conducted since an established testing guideline is currently not available. According to SANCO/10181/2013 –rev. 2.1 13 May 2013, Section 4, in cases where "…agreed test

methods or guidance documents are not yet available for particular data requirements. In these cases, waiving of these particular data requirement points is considered acceptable as long as not test methods or guidance documents are published in form of an update of the Commission Communications 2013/C 95/01 and 2013/C 95/02." In addition, as described in CA 5.8.1, study report DuPont 12062, Revision 1, the hemolytic potential of the metabolite IN-MT713 was evaluated in rats, dogs, and humans. In this study, rats were determined to be the most sensitive species for the most sensitive endpoint, hemolysis. Therefore, since guidelines for an in vitro comparative metabolism study are not yet available, and since an existing study (DuPont 12062) provides data regarding the critical endpoint in the most sensitive species, an in vitro comparative metabolism study has not been conducted at this time."

The RMS is of the opinion that the waiving cannot be accepted based on the argument that no test methods or guidance documents are available. Indeed, these types of studies are widely used for certain chemicals (e.g. pharmaceuticals) and protocols of such studies are publicly available.

It is considered that a comparative *in vitro* metabolism study should have been performed for indoxacarb with at least rat, dog and human materials. The aim of this study would be to determine the relevance of the toxicological animal data for risk assessment.

2.6.2. Summary of acute toxicity

Acute toxicity studies, except by inhalation route, were conducted with DPX-KN128 (99:1) and the results are presented below. Acute toxicity studies were also performed with DPX-MP062 (enantiomeric reaction mass 75:25 S:R) or DPX-JW062 (racemic mixture).

Table 2.6.2-1
Summary of acute toxicity data for indoxacarb (DPX-KN128, DPX-MP062 and DPX-JW062)

Acute Endpoint	DPX-KN128 (99:1)	DPX-MP062 (75:25)	DPX-JW062 (50:50)
Oral LD_{50} (mg/kg bw) Rat	179 (F) [redacted] *1997 - HLO-1997-00055*	268 (F) [redacted] *1996a - HLR 910-96*	-
Dermal LD_{50} (mg/kg bw) Rat	>5000 [redacted] *2003 - DuPont-13019**	>5000 [redacted], *1996b - HLR 798-96*	-
Inhalation LC_{50} (mg/L/4 hours) Rat	-	-	4.2 (F) [redacted], *1995 – HLR 70-95*
Skin irritation Rabbit	Not irritating [redacted] *2003 - DuPont-13164**	Not irritating [redacted], *1997a - HLR 589-96*	-
Eye irritation Rabbit	Not irritating [redacted], *2003 - DuPont-13020**	Not irritating [redacted], *1997b - HLR 588-96*	-
Skin Sensitization Guinea pig Maximisation test	Sensitizer [redacted], *2003 - DuPont-13018**	Sensitizer [redacted], *1996 - HLO 388-96*	-
Buehler test (3-induction)	Not sensitizer [redacted] *2006 – DuPont-18915**	-	-
Phototoxicity Mouse fibroblast cell line Balb/3T3	Not phototoxic *Markell, 2015 – DuPont-43522**	-	-

* Studies newly submitted

Acute oral toxicity study with DPX-KN128 (99:1) resulted in a LD_{50} of 179 mg/kg bw for female rats and 843 mg/kg bw for male rats. The difference in susceptibility between sexes can be explained by the ADME studies where it is shown that the formation of the metabolite IN-JT333 (LD_{50} of 39 mg/kg bw in females, see B.6.8.1) was the major route of metabolism of DPX-JW062 (50:50) in females, whereas in males, 5-HO-JW062 was the most important metabolite. DPX-KN128 (99:1) is therefore classified as Acute Tox. Cat. 3 H301 ("Toxic if swallowed").

DPX-KN128 (99:1) is not acutely toxic via the dermal route of exposure.

No acute toxicity study by inhalation was conducted with DPX-KN128 (99:1). Acute toxicity study by inhalation was available for DPX-JW062 (racemic mixture). The results of the study with DPX-JW062 (50:50) showed that the LC_{50} is greater than 5.4 mg/L in males and equal to 4.2 mg/L in females. The absence of data on DPX-KN128 (99:1) was discussed during the ECHA Committee for Risk Assessment in 2011. In the CLH report, an acute inhalation study with a DPX-MP062 manufacturing used product (MUP) is available and showed a LC_{50} above 5.5 mg/L. Nevertheless, this MUP contains only 70% DPX-MP062 (75:25) equivalent to approximately 52% DPX-KN128 (99:1) on an amorphous silicon dioxide carrier. Given the results of the acute oral toxicity studies performed on DPX-KN128 (99:1) and DPX-MP062 (75:25) showing LD_{50} of the same order of magnitude for both compounds (the acute toxicity of the S-enantiomer (DPX-KN128) might be only slightly higher compared to the R-enantiomer), the results with the racemic mixture are considered also relevant for DPX-KN128 (99:1) (the LC_{50} of DPX-KN128 (99:1) is not expected to be < 1 mg/L given that the LC50 of the racemic mixture is 4.2 mg/L). Therefore, classification as Acute Tox. Cat. 4 H332 ("Harmful if inhaled") was considered appropriate (range 1-5 mg/L).

DPX-KN128 (99:1) was not irritating to skin and to the eyes.

DPX-KN128 (99:1) was found to be a skin sensitiser in a Magnusson and Kligman test but not in a Buehler test. Nevertheless, this Buehler test, using only 3 topical inductions, is not considered sensitive enough to detect skin sensitisers. Therefore, DPX-KN128 (99:1) is classified as Skin Sens. Cat. 1B H317 ("May cause an allergic skin reaction") according to Regulation (EC) No 1272/2008 and its 2nd ATP (category 1B assigned when ≥30% of animals responded at >1% induction dose).

As a conclusion, and in accordance to RAC opinion proposing harmonised classification and labelling of indoxacarb (2011) and Regulation (EU) No 944/2013 (5th ATP of Regulation (EC) No 1272/2008), DPX-KN128 (99:1) should be classified Acute Tox 3 H301, Acute Tox 4 H332 and Skin Sens 1B H317. It is noted that acute toxicity studies performed on DPX-KN128 (99:1) were not available in the CLH report (except acute oral toxicity study). The RAC used the read-across approach to conclude. Nevertheless, in view of the results obtained in these newly submitted studies, the classification adopted by the RAC is confirmed.

DPX-KN128 (99:1) did not show phototoxic potential in the *in vitro* 3T3 NRU phototoxicity test.

2.6.3. Summary of short-term toxicity

The sub-chronic toxicity of DPX-KN128 (coded DPX-JW062-69 in the study report and containing 91.2% of the S-enantiomer), DPX-MP062 (75:25) and DPX-JW062 (50:50) has been evaluated in 90-day feeding studies in rats. DPX-JW062 (50:50) has also been evaluated in 90-day feeding study in mice and 90-day and 1-year feeding study in dogs. A 28-day dermal toxicity study was also performed

on DPX-MP062 (75:25). All these studies were already assessed in the first DAR (2000) or Addendum to DAR (2001).

Table 2.6.3-1
Summary of short-term toxicity studies for indoxacarb (DPX-KN128 (99:1), DPX-MP062 (75:25) and DPX-JW062 (50:50))

Type of study and Test Substance	Dose range tested	NOAEL		LOAEL		Target organ(s) and effects	Reference
		ppm	mg/kg/d	ppm	mg/kg/d		
Oral (Feeding), 90-day Rat DPX-JW062-69 [91.2% DPX-KN128 and 0.3% DPX-KN127]	M: 0, 8, 20, 50, 100, 200 ppm – 0, 0.56, 1.4, 3.2, 6.6, 14 mg/kg bw/d F: 0, 3, 8, 20, 50, 100 ppm – 0, 0.25, 0.68, 1.7, 4.1, 8.5 mg/kg bw/d	M: 20 F: 8	M: 1.4 F: 0.68	M: 50 F: 20	M: 3.2 F: 1.7	At LOAELs: haemolytic effects on circulating RBC (*up to -6% and -9% decreases in M and F respectively, Met-Hb in M*) and histopathological spleen effects. At higher doses: decreased body weights, body weight gains, food consumption, increased MCV and/or reticulocytes, methaemoglobinemia, histopathological findings in the liver and bone marrow.	[redacted] 1997a HLR 301-94, Revision No. 2
Oral (Feeding), 90-day - rat DPX-MP062 (75:25)	M: 0, 10, 50, 100, 200 ppm – 0, 0.62, 3.09, 6.01, 15.0 mg/kg bw/d F: 0, 10, 25, 50, 100 ppm – 0, 0.76, 2.13, 3.78, 8.94 mg/kg bw/d	M: 10 F: <10	M: 0.62 F: <0.76	M: 50 F: 10	M: 3.09 F: 0.76	At LOAELs: haemolytic effects on circulating RBC (*up to -6% and -7% decreases in M and F respectively*) and histopathological spleen effects At higher doses: decreased body weights, body weight gains, food consumption, increased MCV, decreased total protein and globulin concentrations (M), histopathological findings in the liver, kidney, thymus and bone marrow. At 100 ppm only, in F: mortality	[redacted] 1997 HL-1997-00056, Revision No. 1
Oral (Feeding), 90-day - Rat DPX-JW062 (50:50)	M: 0, 30, 60, 125, 250 ppm – 0, 1.9, 3.9, 8.0, 16 mg/kg bw/d F: 0, 15, 30, 60, 125 ppm – 0, 0.99, 2.3, 4.6, 9.5 mg/kg bw/d	M: <30 F: 15	M: <1.9 F: 0.99	M: 30 F: 30	M: 1.9 F: 2.3	At LOAELs: haemolytic effects on circulating RBC (*up to -7% and -9% decreases in M and F respectively*) and histopathological spleen effects At higher doses: decreased body weights, body weight gains, food consumption, increased MCV and reticulocytes, histopathological findings in the liver and bone marrow	[redacted] 1997b HLR 751-93, Revision No. 2
Oral (Feeding), 90-day – with reversibility Rat DPX-JW062 (50:50)	M: 0, 30, 60, 125, 250 ppm - 0, 1.8, 3.7, 7.5, and 15 mg/kg bw/day F: 0, 15, 30, 60, 125 ppm - 0, 1.2, 2.5, 4.9, and 12 mg/kg bw/day	Not applicable*		Not applicable*		Haematological effects (decreased RBC, Hb, Ht, and increased MCV) were reversible for both males and females within the 21-day recovery period. **The study did not include ophthalmology, clinical chemistry, urinalysis, organ weighing, and histopathology and was designed to assess the reversibility of haematological effects.*	[redacted] 1998 HL-1998-01200

Oral (Feeding), 90-day - Mouse DPX-JW062 (50:50)	0, 35, 75, 150, 10/300 ppm M: 0, 5.5, 12, 23, 1.7/44 mg/kg bw/d F: 0, 7.0, 16, 30, 2.1/51	M: 35 F: 35	M: 5.5 F: 7.0	M: 75 F: 75	M: 12 F: 16	At LOAELs: slight haemolytic effects on circulating RBC, Heinz bodies, increased reticulocytes and histopathological spleen effects At higher doses: decreased body weights, body weight gains, food consumption, histopathological findings in the liver, clinical signs indicative of neurotoxicity	[redacted] 1997 HLR 750-93, Revision No. 1
Oral (Feeding) 90-day Dog DPX-JW062 (50:50)	0, 40, 80, 160, 640 ppm M: 0, 1, 2, 5, 18 mg/kg bw/d F: 0, 1, 3, 5, 17 mg/kg bw/d	M: <40 F: <40	M: <1 F: <1	M: 40 F: 40	M: 1 F: 1	At LOAELs: haemolytic effects on circulating RBC (*up to -14% and -13% decreases in M and F respectively, increased MCV*) and histopathological effects in spleen, liver, kidney, bone marrow At higher doses: Heinz bodies, increased bilirubin levels, increased phosphatase alkaline and liver weights in F	[redacted] 1997a HLO 494-95, Revision No. 3
Oral (Feeding) 1-year dog study DPX-JW062 (50:50)	0, 40, 80, 640, 1280 ppm M: 0, 1.1, 2.3, 17.5, 33.6 mg/kg bw/d F: 0, 1.3, 2.4, 18.9, 36.1 mg/kg bw/d	M: <40 F: <40	M: <1.1 F: <1.3	M: 40 F: 40	M: 1.1 F: 1.3	At LOAELs: haemolytic effects on circulating RBC (*up to -14% and -3% decreases in M and F respectively, increased MCV and/or reticulocytes*) and histopathological effects in spleen, liver, kidney, bone marrow, increased plasma bilirubin levels, bilirubinuria At higher doses: Heinz bodies, increased phosphatase alkaline and liver weights	[redacted] 1997b HLO 885-96, Revision No. 1
Dermal, 28-day - Rat DPX-MP062 (75:25)	0, 50, 500, 1000, 2000 mg/kg bw/d	_	M: <50 F: <50	_	M: 50 F: 50	At LOAELs: slight haemolytic effects and histopathological spleen effects At higher doses: decreased body weights, body weight gains, food consumption, increased MCV and/or reticulocytes, methaemoglobinemia, increased spleen weights	[redacted] 1999 DuPont-2813

Sub-chronic studies in rats (90-day feeding studies in rats) demonstrate that the insecticides DPX-KN128 (99:1), as well as DPX-MP062 and DPX-JW062 (containing the isomers DPX-KN128 and IN-KN127 in ratios of approximately 75:25 and 50:50, respectively) have similar toxicities at their low-effect levels. The LOAELs in rats were based on haemolytic effects. At the LOAELs, the haemolytic effects typically consisted of decreases in number of erythrocytes, haemoglobin concentration, and haematocrit, accompanied by secondary changes in the spleen such as increased haemosiderin pigments. At higher dose levels, histopathological secondary changes were also reported in liver, kidneys and bone marrow, and clinical chemistry findings were also noted.

Increased reticulocyte counts and MCV observed at highest dose levels are indicative of a regenerative anaemia. Moreover, in the only 90-day study in which Met-Hb was measured (study conducted on DPX-KN128), its level was found to be increased. It is to be noted that Heinz bodies were not measured in the 90-day rat studies. Regenerative responses were evident in peripheral blood (increased MCV, reticulocyte counts) and also in spleen (increased extramedullary haemopoiesis) and bone marrow (mixed cell hyperplasia). Consistent with the regenerative nature of these effects, the 90-day reversibility feeding study in rats with DPX-JW062 (50:50) demonstrated that haematologic effects (decreased RBC, Hb, Ht and increased MCV) were reversible within 21 days (the earliest recovery

interval assessed). Nevertheless, the study design did not allow demonstrating the reversibility of histopathological findings.
Statistical modelling of the haematologic effects in subchronic studies with DPX-MP062 (75:25), DPX-JW062 (50:50), and DPX-KN128 (99:1) demonstrated that the magnitude of the haematologic effects were similar irrespective of the isomer blend (Green, 1999/DuPont-2780, see B.6.8.2).

The other effects commonly observed in rats administered DPX-KN128 (99:1), DPX-MP062 (75:25) or DPX-JW062 (50:50) were decreased body weight gains, body weights and food consumption.

Mortality was also observed in one of the three 90-day rat studies. Five out of ten females administered 100 ppm of DPX-MP062 (75:25) (equivalent to 8.94 mg/kg bw/d) died during the course of the study (between test days 8 and 19). The decedent rats had atrophy of the spleen, thymus and/or bone marrow at necropsy, and haemoglobin pigment was found in the renal tubule cells and/or lumens. Therefore, it could not be ruled out that these deaths are related to haematotoxicity. It should be noted that mortality was also reported in other studies: in the 28-day studies at the dose levels of 23.5 mg/kg bw/d in 2/5 female rats and at 34 and 35.3 mg/kg bw/d in 1/10 male and 1/10 female mice respectively; in the subchronic oral neurotoxicity study at the dose level of 6.09 mg/kg bw/d in 3/12 female rats on test days 9-12; in the developmental neurotoxicity study at the dose level of 3 mg/kg bw/d in 3/25 female rats showing also clinical signs of neurotoxicity, on gestation day 19 to lactation day 3.

Overall, females appeared to be more sensitive to the effects of indoxacarb than males. This is in agreement with ADME data which showed gender differences in absorption and biotransformation of indoxacarb (see B.6.1).

Sub-chronic feeding studies have also been conducted in mice with DPX-JW062 (50:50). Effects seen were qualitatively similar to those observed in rats: haemolytic effects accompanied by secondary histopathological spleen effects were observed at the LOAEL. Mice were less sensitive to the subchronic toxicity of DPX-JW062 (50:50) relative to the rat and dog. Body weight and nutritional effects, as well as clinical signs suggestive of neurotoxicity (see B.6.7), were also reported at higher dose levels.

Repeated dose toxicity studies were conducted with DPX-JW062 (50:50) in dogs. The LOAELs in the 90-day and 1-year dog studies with DPX-JW062 (50:50) were also based on haemolytic anaemia: decreases in number of erythrocytes, haemoglobin concentration, and haematocrit, accompanied by secondary changes in the spleen, liver, kidney and bone marrow. The pattern of changes in the mean values of the erythrocyte indices (MCV, MCH, and MCHC), platelet counts, and reticulocyte counts indicated that the anaemia was regenerative. At higher dose levels, increased numbers of Heinz bodies (parameters only measured in the dog studies) indicated that oxidative denaturation of haemoglobin may have been the cause of haemolysis. No NOAELs can be determined in these dog studies.

A sub-chronic dermal toxicity study was conducted in rats with DPX-MP062 (75:25). Similar effects than those observed after oral administration were observed from the low dose level of 50 mg/kg bw/d on haematology endpoints (decreased red blood cell parameters and secondary changes in the spleen in the majority of the animals). No unique additional target organs were detected. Based on the lower systemic toxicity from dermal exposure and the similarity of the systemic response compared to the oral route of exposure, sub-chronic dermal toxicity studies were not conducted with DPX-JW062 (50:50) or DPX-KN128 (99:1).

Based on the mortality observed in females in the 90-day rat study with DPX-MP062 (75:25), supported by the mortality data of the 28-day rat and mouse studies with DPX-JW062 (50:50), and based on the haemolytic anemia observed in the subchronic studies with DPX-KN128 (99:1), DPX-MP062 (75:25) and DPX-JW062 (50:50) and the dose levels at which these effects occured, a

classification STOT-RE Category 1 was adopted by the ECHA Committee for Risk Assessment (2011).

Interpretation of haematological effects:
During the peer review process for inclusion of indoxacarb in Annex I of Directive 91/414/EEC, the critical effects to take into account for the setting of the NOAELs were deeply discussed between Member States during the years 2000-2005. Based on the same toxicological database, the JMPR (2005) came to different conclusions than those taken at EU level. In view of these discrepancies, the Commission requested the RMS NL to write an addendum to re-evaluate the derivation of the ADI. This post-approval addendum was available in 2007.

As described in this post-approval addendum prepared by NL, the evaluation of the haematological effects in the EU and by the JMPR was as follows:

- EU: "*In the evaluation of the effects on circulating red blood cells in the individual studies, a slight but significant decrease in one of the parameters of circulating erythrocyte numbers (RBC count, Hb, Ht) was considered as adverse. It is however recognized that a very slight but significant deviation in one circulating red blood cell parameter, in the absence of other effects (increased haemosiderin pigment in liver, kidneys, spleen and bone marrow, presence of Heinz bodies and met-Hb, increased serum bilirubin values, absence of regenerative responses (increased MCV and reticulocyte counts, extramedullary haemopoiesis and mixed cell hyperplasia in bone marrow)), is likely to be fortuitous. Furthermore, dose-dependency naturally plays an important role in assessing the adversity of the effects. Unfortunately, in the available studies the existence of a dose-response relationship was obscured by the small differences in the dose levels.*
Keeping this in mind and comparing all available data with DPX-MP062 (enriched isomer mixture) and DPX-JW062 (racemic mixture), it is concluded that the overall NOAEL for DPX-MP062 for short- and long-term exposure would be 10 ppm for male and female rats, equivalent to 0.6 mg/kg bw. This 'overall NOAEL' for DPX-MP062 of 0.6 mg/kg bw is used to derive the AOEL and ADI."

- JMPR: "*The 2005 JMPR considered the establishment of an ADI and ARfD for indoxacarb. The Joint Meeting concluded that the mild haemolysis observed in studies in rats and dogs given repeated doses was characterized by a reduced erythrocyte count, erythrocyte volume fraction, haemoglobin concentration, and a secondary physiological response involving increased haemopoiesis and deposition of haemosiderin in the spleen and liver. While the reductions in erythrocyte numbers through oxidative damage of haemoglobin occurred with a rather shallow dose–response curve, they achieved statistical significance relative to concurrent controls. However, the JMPR considered that these small changes in circulating erythrocyte mass in the absence of a concomitant increase in haematopoeisis were of no toxicological importance. As a consequence, the ADI of 0–0.01 mg/kg bw per day was based on a NOAEL of 1.1 mg/kg bw per day for erythrocyte damage, Heinz body formation and the secondary increase in haematopoeisis in the spleen and liver in a 1-year dietary study in dogs and using a 100-fold safety factor. This NOAEL was supported by a similar value (1.3 mg/kg bw per day) in a two-generation study of reproduction in rats in which reduced body-weight gain and food consumption in dams was observed. At higher doses, the pups had reduced bodyweight gain during lactation*."

Therefore, the RMS NL re-evaluated some of the critical studies in the post-approval addendum:
"Different opinions are found among scientists whether anaemia itself is a critical effect or that the adaptation to the anaemia (higher MCV of red blood cells, increase of haematopoiesis, appearance of Heinz bodies) is the critical effect.
In the EU-DAR, a statistically significant and dose-dependent decrease in one or more indicators of circulating erythrocyte mass was considered to be an adverse effect (also when the decrease was <10%), and the simultaneous occurrence of a regenerative response was not considered a prerequisite for this judgement.

The JMPR considered that small changes in circulating erythrocyte mass in the absence of a concomitant increase in haematopoeisis were of no toxicological importance.
In the current re-evaluation of indoxacarb, the RMS agrees with the JMPR that the evaluation in the EU-DAR has been conservative and that a mild anaemia alone, without a regenerative response, should not be considered as adverse. In this addendum, the RMS used the following criteria to determine whether the haematological effects are adverse or not:
- a statistical significant decrease in RBC count, Hb or Ht, higher than 10%, is considered adverse
- a statistical significant decrease in RBC count, Hb or Ht, in combination with a regenerative response (higher MCV of red blood cells, higher reticulocyte count, increase of haematopoiesis, appearance of Heinz bodies, increased pigment) is considered adverse."

In the sake of transparency, the RMS FR has included at the end of each study:
- the conclusions from the original DAR,
- the conclusions from the post-annex I addendum (if available) which take into account the JMPR evaluation,
- the conclusions proposed by the applicant in the renewal dossier,
- the conclusions proposed by the RMS FR in the context of the renewal of the active substance.

The RMS FR is in general in agreement with the assessment proposed by the RMS NL in the post-approval addendum. To determine the LOAELs of each study, the following criteria were considered adverse:
- a decrease in red blood cell count, haemoglobin concentration and/or haematocrit higher than 10%. As highlighted in the JMPR Guidance Document for WHO monographers and reviewers (2015), a decrease in haemoglobin value by more than about 10% is a starting point to judge anaemia.
- a decrease in red blood cell count, haemoglobin concentration and/or haematocrit around 10% but associated with at least one of the following effect:
- increased mean corpuscular volume greater than 5% (according to JMPR Guidance Document 2015)
- increased reticulocyte count
- increased level of methaemoglobin greater than 5% in dogs and 1.5% in rats (according to JMPR Guidance Document 2015). This parameter was nevertheless only measured in the 90-day rat study conducted on DPX-KN128 (99:1).
- increased haemosiderin deposits in the spleen, liver, kidney and/or bone marrow compared to the control group. Indeed, according to Muller at al. (2006)[1], *"Since a low extent of haemosiderosis is a normal age-related lesion that may show some degree of interindividual variation, only clear increases in haemosiderin deposition compared to the internal control group should be considered as treatment-related effects"*.
- increased haematopoiesis
- appearance of Heinz bodies. This parameter was nevertheless only measured in the 90-day and 1-year dog studies.

The applicant proposed other criteria for assessment of haematologic effects (see Volume 3B6).

2.6.4. Summary of genotoxicity

Genotoxicity studies were conducted with DPX-KN128 (99:1) and DPX-MP062 (75:25). Summaries of these studies are presented below.

Table 2.6.4-1

[1] Muller A. et al., Hazard classification of chemicals inducing haemolytic anaemia: an EU regulatory perspective. Regulatory toxicology and Pharmacology 45 (2006) 229-241

Summary of genotoxicity studies for indoxacarb (DPX-KN128 and DPX-MP062)

Type of study	Test system	Concentration range tested	Result	Reference
***In vitro* bacterial mutagenicity (Ames)**				
DPX-KN128 (99:1)	*Salmonella typhimurium* and *Escherichia coli*	0 - 5000 µg/plate (with and without S9)	Negative	Wagner 2004 DuPont-14332*
DPX-MP062 (75:25)	*Salmonella typhimurium* and *Escherichia coli*	0 - 5000 µg/plate (with and without S9)	Negative	Mathison 1997 HLR 831-96
***In vitro* mammalian cell gene mutation (CHO/HGPRT)**				
DPX-KN128 (99:1)	CHO cells	0 - 50 µg/mL (with and without S9)	Negative	San and Clarke 2003 DuPont-13023*
DPX-MP062 (75:25)	CHO cells	0 - 250 µg/mL (with and without S9)	Negative	San and Clarke 1997 HLO-1997-00030
***In vitro* chromosome aberration**				
DPX-KN128 (99:1)	Human lymphocytes	0 – 75 µg/mL with S9 0 – 50 µg/mL without S9	Negative	Gudi and Rao 2004 DuPont-13022, Revision No. 1*
DPX-MP062 (75:25)	Human lymphocytes	0 - 1000 µg/mL (with and without S9)	Negative	Gudi and Schadly 1996a HLO 979-96
***In vitro* unscheduled DNA synthesis**				
DPX-MP062 (75:25)	Rat primary hepatocytes	0 - 200 µg/mL	Negative	San and Sly 1997a HLO-1997-00033
***In vivo* micronucleus**				
DPX-KN128 (99:1)	Mouse bone marrow	0, 500, 1000, 2000 mg/kg bw	Negative	[redacted] 2003 DuPont-13021*
DPX-MP062 (75:25)	Mouse bone marrow	0, 3000, 4000 mg/kg bw (M) 0, 1000, 2000 mg/kg bw (F)	Negative	[redacted] 1997 HLR 1046-96

* Studies newly submitted

DPX-KN128 (99:1) did not induce mutations in bacteria or mammalian cells *in vitro*, and did not induce structural chromosomal aberrations or polyploidy in mammalian cells *in vitro* either in the presence or in the absence of metabolic activation. DPX-KN128 (99:1) did not induce an increase in micronucleated polychromatic erythrocytes in bone marrow of mice. The same results are reported for the 75:25 S:R enantiomeric blend DPX-MP062. DPX-MP062 (75:25) also did not cause unscheduled DNA synthesis in primary rat hepatocytes *in vitro*.

As a conclusion, the available data indicate that DPX-KN128 (99:1) and DPX-MP062 (75:25) did not show a genotoxic potential.

Photogenotoxicity potential:

No photogenotoxicity assay was provided for indoxacarb.

The following justification was provided by the applicant: "*This study was not conducted since an established testing guideline is currently not available. According to SANCO/10181/2013 –rev. 2.1 13 May 2013, Section 4, in cases where "...agreed test methods or guidance documents are not yet available for particular data requirements. In these cases, waiving of these particular data*

requirement points is considered acceptable as long as not test methods or guidance documents are published in form of an update of the Commission Communications 2013/C 95/01 and 2013/C 95/02." In addition, Indoxacarb was negative in the phototoxicity assay at the limit of solubility (MCA 5.2.7), and was negative in all in vitro and in vivo genotoxicity assays (MCA 5.4.4), and no further testing is warranted based on these results. Further, according to the attached publication by Lynch et al, (2011), the International Workshop of Genotoxicity Testing has concluded that photogenotoxicity testing should no longer be recommended as part of the standard photosafety testing strategy."

The RMS agreed with the applicant. However, according to Regulation (EU) no 283/2013, a photomutagenicity test would not be required for indoxacarb as its Ultraviolet/visible molar extinction/absorption coefficient is less than 1 000 L × mol^{-1} × cm^{-1}.

2.6.5. Summary of long-term toxicity and carcinogenicity

The chronic toxicity and/or carcinogenicity of DPX-JW062 (50:50) were evaluated in rats and mice. These studies were already available in the first DAR (2000). According to the applicant, since DPX-JW062 (50:50) was not carcinogenic in rats or mice, and DPX-MP062 (75:25) and DPX-KN128 (99:1) technical actives were not genotoxic, and the primary metabolites IN-JT333 and IN-KG433 were also not genotoxic, chronic studies were not repeated with DPX-MP062 (75:25) or DPX-KN128 (99:1) technical actives.

Table 2.6.5-1
Summary of long-term toxicity studies for indoxacarb (DPX-JW062)

Type of study	Dose range tested	NOAEL		LOAEL		Target organ(s) and effects	Reference
		ppm	mg/kg/d	ppm	mg/kg/d		
Oral (Feeding), 2 - year Rat DPX-JW062 (50:50)	M: 0, 20, 40, 60, 125, 250 ppm – 0, 0.798, 1.59, 2.40, 5.03, 10.0 mg/kg bw/d F: 0, 10, 20, 40, 60, 125 ppm – 0, 0.554, 1.04, 2.13, 3.60, 7.83 mg/kg bw/d	M: 40 F: 20	M: 1.59 F: 1.04	M: 60 F: 40	M: 2.40 F: 2.13	At LOAELs: haemolytic effects on circulating RBC and histopathological effects in the liver and spleen At higher doses: decreased body weights, body weight gains, histopathological findings in the kidney and bone marrow, increased spleen weights No carcinogenic potential.	[redacted] 1997a HLR 1174-96, Revision No. 1

Oral (Feeding), 18-month Mouse DPX-JW062 (50:50)	M: 0, 20, 100, 200/150/125 – 0, 2.63, 13.8, 32.2/22.7/17.0 mg/kg bw/d F: 0, 20, 100, 200/150/125 ppm – 0, 3.99, 20.3, 44.1/31.4/23.7 mg/kg bw/d	M: 20 F: 20	M: 2.63 F: 3.99	M: 100 F: 100	M: 13.8 F: 20.3	At LOAELs: decreased body weights, body weight gains and food efficiency, clinical signs indicative of neurotoxicity At higher doses: mortality, histopathological findings in heart (myocardial necrosis and haemorrhage in males) and brain (neuronal degeneration/necrosis in males and females) No carcinogenic potential.	[redacted] 1997 HLR 799-96

DPX-JW062 (50:50) did not elicit an oncogenic response in rats or mice at any dose level tested.
According to the co-RMS (ES), "*The toxicokinetics and overall metabolism of DPX MP062 and DPX JW062 showed quantitative differences; moreover, according to the available data DPX-MP062 (75:25) seems to be more absorbed in female rats than DPX-JW062 (50:50). From a theoretical point of view, the greater amount of the S-isomer in DPX-KN128 would lead to an increase of metabolite IN-JT333 and consequently prolonged and more markedly effects in female rats could be expected. In view of the available data for long-term and carcinogenesis (there are only studies with the 50:50 proportion of the enantiomers) the carcinogenic potential of indoxacarb can´t totally excluded given the higher proportion of S-enantiomer in DPX-KN128.*"
The RMS acknowledged that carcinogenicity studies were only performed with the racemic mixture DPX-JW062 (50:50). Nevertheless, given that:

- no neoplastic lesions were observed in the rat and mouse long-term studies with DPX-JW062 (50:50);
- DPX-KN128 (99:1) and DPX-MP062 (75:25) did not show genotoxic potential;
- the metabolite IN-JT333 did not show genotoxic potential;
- DPX-JW062 (50:50), DPX-MP062 (75:25) and DPX-KN128 (99:1) showed similar adverse effects at similar range of dose levels. No additional target organ was identified with the pure enantiomer DPX-KN128;

it is considered unlikely that DPX-KN128 would be a carcinogenic substance.

In rats, test substance-related effects comprised haematological effects indicative of haemolytic anaemia, i.e., decreases in RBC counts, Hb and Ht, accompanied with indications of increased hematopoiesis (spleen), increased haemosiderin accumulation (liver, spleen, kidneys), splenic congestion, increased spleen weights and bone marrow hyperplasia. The decreases in RBC, Hb, and Ht were generally greater than 10% of the control values in the 40, 60 and 125 ppm female groups during the first 18 months of the study. In males, decreases of red blood cell mass parameters were more pronounced at 125 and 250 ppm the first 6 months of treatment. After 24-months mean RBC, Hb and Ht were comparable with or higher than control values.
Increased mortality was seen in females of the top dose group (125 ppm equivalent to 7.83 mg/kg bw/d) prior to interim sacrifice. Decedent females showed bone marrow atrophy, thymic necrosis and splenic lymphoid depletion. Decreased body weights and body weight gains were observed from 60 ppm in females and 125 ppm in males.
The NOAEL of this study is set at 20 ppm in females (1.04 mg/kg bw/d) and 40 ppm in males (1.59 mg/kg bw/d).

In mice, effects at 100 ppm (13.8 mg/kg bw/d in males and 20.3 mg/kg bw/d in females) and above comprised decreased body weight, body weight gain, and food efficiency, and clinical signs suggestive

of neurotoxicity (abnormal gait and/or mobility, and tilt head) in male and female mice. Effects at the top dose level included increased mortality and histopathological findings in heart (myocardial necrosis and haemorrhage in males) and brain (neuronal degeneration/necrosis in males and females). No substance-related effects were seen at 20 ppm (equal to 2.63 mg/kg bw/day in males and 3.99 mg/kg bw/day in females).
Based on the finding of myocardial necrosis observed in this long-term mouse study from ≥ 17 mg/kg bw/d, a classification as STOT-RE was adopted by the ECHA Committee for Risk Assessment (2011).

2.6.6. Summary of reproductive toxicity

A two-generation reproduction study was conducted in rats with DPX-JW062 (50:50). Developmental studies in the rat and rabbit were conducted with DPX-JW062 (50:50). Developmental studies in rats were also conducted with DPX-MP062 (75:25) and DPX-KN128 (99:1).

Table 2.6.6-1
Summary of reproductive toxicity data for indoxacarb (DPX-KN128, DPX-MP062 and DPX-JW062)

Type of study and test substance	Doses/ concentrations tested	NOAEL	LOAEL	Target organ(s) and effects	Reference
Multigeneration reproduction Rat DPX-JW062 (50:50)	0, 20, 60, 100 ppm in the diet Eq. to 1.2, 3.7 and 6.1 mg/kg bw/d	Parental: 20 ppm = 1.2 mg/kg bw/d Repro/Fertility: 100 ppm 6.1 mg/kg bw/d Offspring: 20 ppm = 1.2 mg/kg bw/d	Parental: 60 ppm = 3.7 mg/kg bw/d Repro/Fertility: >100 ppm > 6.1 mg/kg bw/d Offspring: 60 ppm = 3.7 mg/kg bw/d	Parental: decreased body weight gains and food consumption in F0 females, increased spleen weight in F0 and F1 females Offspring: decreased F1 pup body weights during lactation	[redacted] 1997 HLO 115-96, Revision No. 2
Developmental Rat DPX-KN128 (99:1)	0, 0.5, 1, 2, 3.5 mg/kg/day In PEG by gavage GD 6-20	Maternal: 0.5 mg/kg bw/d Developmental: 2 mg/kg bw/d	Maternal: 1 mg/kg bw/d Developmental: 3.5 mg/kg bw/d	Maternal: decreased body weight gains Developmental: decreased fetal weights	[redacted] 2004 DuPont-12748*
Developmental Rat DPX-MP062 (75:25)	0, 0.5, 1, 2, 4 mg/kg/day In PEG by gavage GD 7-21	Maternal: 2 mg/kg bw/d Developmental: 2 mg/kg bw/d	Maternal: 4 mg/kg bw/d Developmental: 4 mg/kg bw/d	Maternal: decreased body weights, body weight gains and food consumption Developmental: decreased fetal weights	[redacted] 2005 HL-1997-00202, Revision No. 2
Developmental Rat DPX-JW062 (50:50)	0, 10, 100, 500, 1000 mg/kg/day In methylcellulose by gavage GD 7-21	Maternal: 10 mg/kg bw/d Developmental: 10 mg/kg bw/d	Maternal: 100 mg/kg bw/d Developmental: 100 mg/kg bw/d	Maternal: decreased body weight, body weight gains and food consumption, clinical signs, mortality and GI tract macroscopic findings Developmental: decreased mean number of live foetuses per litter. At higher doses: decreased mean fetal weights	[redacted] 1997 HL-1997-00049

Developmental Rabbit DPX-JW062 (50:50)	0, 250, 500, 1000 mg/kg/day In methylcellulose by gavage GD 7-28	Maternal: 500 mg/kg bw/d Developmental: 500 mg/kg bw/d	Maternal: 1000 mg/kg bw/d Developmental: 1000 mg/kg bw/d	Maternal: decreased body weights, body weight gains and food consumption Developmental: decreased mean fetal weights and retarded sternebral ossification	[redacted] 1995 HLR 587-95

* Studies newly submitted

In an oral 2-generation reproduction toxicity study with DPX-JW062 (50:50) in rats, the NOAEL for parental toxicity was established at 1.2 mg/kg bw/day, based on effects on body weight, food consumption, and organ weights (especially the spleen) observed at higher dose levels. Because of decreased pup weights during lactation, the NOAEL for offspring toxicity was set at 1.2 mg/kg bw/day as well. No reproduction toxicity was observed up to 100 ppm (6.1 mg/kg bw/day).

Prenatal developmental toxicity studies were performed in rats with DPX-KN128 (99:1), DPX-MP062 (75:25) and DPX-JW062 (50:50) and in rabbits with DPX-JW062 (50:50). No indications for a teratogenic potential of the test compounds were observed in these studies.
In the rat study conducted with DPX-KN128 (99:1), the maternal NOAEL is set at 0.5 mg/kg bw/d, based on the decreased body weight gains observed from the dose level of 1 mg/kg bw/d (-62% during GD6-8 and -11% during GD6-21). The developmental NOAEL is 2 mg/kg bw/d, based on decreased fetal weight observed at the dose level of 3.5 mg/kg bw/d.
Maternal and developmental NOAELs were determined to be 2 mg/kg bw/d for DPX-MP062 (75:25), based on decreased body weights, body weight gains and food consumption in the dams and decreased weights of the fetuses.
With DPX-JW062 (50:50), maternal and developmental NOAELs were set at 10 mg/kg bw/d. From the dose level of 100 mg/kg bw/d, decreased body weight, body weight gains and food consumption, as well as clinical signs, mortality and GI tract macroscopic findings were observed in dams and decreased number of live fetuses per litter was also noted. Decreased mean fetal weights occurred at 500 mg/kg bw/d and above.
In an oral developmental toxicity study in rabbits with DPX-JW062 (50:50), the NOAEL for maternal and developmental toxicity were both established at 500 mg/kg bw/day, based on decreased body weight, body weight gains and food consumption in dams and decreased fetal weights and retarded sternebral ossification in fetuses.

It is important to note that the differences in NOAELs observed between DPX-MP062 (75:25) and DPX-JW062 (50:50) in the teratogenicity studies in rats may be due to differences in bioavailability influenced by the dosing vehicle. Indeed, in two pilot teratogenicity studies in rats in which both compounds were dissolved in polyethylene glycol (PEG 400) comparable (provisional) NOAELs were established for both maternal and developmental toxicity (DPX-MP062 (75:25) respective NOAELs 1 and 4 mg/kg bw/d; DPX-JW062 (50:50) respective NOAELs 1.5 and 6 mg/kg bw/d), which are in the same order of magnitude than NOAELs obtained with DPX-KN128 (99:1) and DPX-MP062 (75:25) dissolved in PEG. On the contrary, NOAELs determined for DPX-JW062 (50:50) dissolved in methylcellulose amount to 10 mg/kg bw/d.

Developmental studies with DPX-JW062 (50:50) administered in methylcellulose demonstrated that the rat was more susceptible than the rabbit to the systemic toxicity of the compound. The NOAELs for both maternal and foetal toxicity in the rat was 10 mg/kg/day as compared to 500 mg/kg/day in the rabbit.

It is noted that haemotological effects, identified as the critical endpoint in oral short-term and long-term toxicity studies, were not addressed in the reproduction and teratogenicity studies.

2.6.7. Summary of neurotoxicity

An acute and a 90-day rat neurotoxicity studies were performed on DPX-MP062 (75:25). A newly submitted rat developmental neurotoxicity study was carried out on DPX-KN128 (99:1).

Table 2.6.7-1
Summary of neurotoxicity studies for indoxacarb (DPX-KN128 and DPX-MP062)

Type of study and test substance	Doses/ concentrations tested	NOAEL	LOAEL	Target organ(s) and effects	Reference
Acute neurotoxicity (Gavage), Rat DPX-MP062 (75:25)	M: 0, 25, 100, 200 mg/kg F: 0, 12.5, 50, 100 mg/kg	Neurotoxicity: M: 100 mg/kg bw F: 50 mg/kg bw Systemic: M: 100 mg/kg bw F: 12.5 mg/kg bw	Neurotoxicity: M: 200 mg/kg bw F: 100 mg/kg bw Systemic: M: 200 mg/kg bw F: 50 mg/kg bw	Neurotoxicity: decreased forelimb grip strength and decreased foot splay in males; decreased motor activity in females Systemic: decreased body weight gains, body weights and food consumption	[redacted] 2001 HLR 1117-96, Revision No. 2
Subchronic neurotoxicity (Feeding), 90-d Rat DPX-MP062 (75:25)	M: 0, 10, 100, 200 ppm – 0, 0.569, 5.62, 11.9 mg/kg bw/d F: 0, 10, 50, 100 ppm – 0, 0.685, 3.30, 6.09 mg/kg bw/d	Neurotoxicity: M: 200 ppm 11.9 mg/kg bw/d F: 100 ppm 6.09 mg/kg bw/d Systemic: M: 10 ppm 0.57 mg/kg bw/d F: 10 ppm 0.685 mg/kg bw/	Neurotoxicity: M: >200 ppm >11.9 mg/kg bw/d F: >100 ppm >6.09 mg/kg bw/d Systemic: M: 100 ppm 5.62 mg/kg bw/d F: 50 ppm 3.30 mg/kg bw/d	Neurotoxicity : no effect Systemic: decreased body weights, body weight gains and food consumption. Higher dose: mortality in F	[redacted] 1997 HLR 1116-96, Revision No. 1
Developmental Neurotoxicity Rat DPX-KN128 (99:1)	0, 0.5, 1, 1.5, 3.0 mg/kg/day In PEG by gavage GD 6 – LD10 for dams PND 11-20 for F1 pups	Maternal: 1 mg/kg bw/d Developmental: 1.5 mg/kg bw/d	Maternal: 1.5 mg/kg bw/d Developmental: 3.0 mg/kg bw/d	Maternal: decreased body weight gains. At 3 mg/kg bw/d: mortality, clinical signs of neurotoxicity Developmental: increased number of stillborn pups, increased pup mortality on PND1 to 4 and decreased pup weight per litter on PND0	[redacted] 2006a and 2006b DuPont 15150 and DuPont 15150 Supplement No. 1*

* Studies newly submitted

In an acute study and in a 90-day feeding study, neurotoxicity of DPX-MP062 (75:25) was assessed in rats using a functional observational battery, motor activity measurements, and neuropathological examinations of nerve tissues and muscle.

No evidence of neurotoxicity was observed in the 90-day study whereas clinical signs indicating neurodysfunction were reported in the acute study and consisted of decreased forelimb grip strength and decreased foot splay in males at 200 mg/kg bw and decreased motor activity in females at 100 mg/kg bw. According to RAC opinion, although these effects were observed at doses below guidance value for STOT SE 1 (<300 mg/kg bw), they occurred at doses that are also relevant to induce lethality. Indeed, in the acute oral toxicity study with DPX-KN128 (99:1), the LD50 is 179 mg/kg bw in females and clinical signs included hypoactivity, ataxia or impaired righting reflex. It can be expected that these effects indicate severe moribundity and are mortality-related. As indoxacarb is

already classified for acute oral toxicity, data were not considered to justify a classification for STOT-SE.

It should be noted that neurotoxicity findings were observed in the repeated-dose toxicity studies performed in mice with the racemic mixture DPX-JW062 (50:50). Indeed, clinical signs indicative of neurotoxicity were reported in the 18-month study at 100 ppm and above in males and females (13.8 mg/kg bw/d), in the 90-d study at 150 ppm and above in females (30 mg/kg bw/d) and at 300 ppm in males (44 mg/kg bw/d) and in the 28-day study at 118 ppm and above in males and females (17.9 mg/kg bw/d). In the long-term mouse study, low incidences of neuronal degeneration/necrosis occurred in the brain of male and female mice at the highest dietary level, and in a female mouse at 100 ppm (20.3 mg/kg bw/d). The primary sites affected were the piriform cortex and the hippocampus. A more chronic brain lesion, diagnosed as residual vacuolation, was present in the piriform cortex of two high-concentration (23.7 to 44 mg/kg bw/d) females sacrificed at the termination of the study.

As a consequence, indoxacarb was classified as STOT RE for effects on the nervous system by the ECHA Committee for Risk Assessment (2011).

Clinical signs of neurotoxicity were also observed in rats in the newly submitted developmental neurotoxicity study conducted with DPX-KN128 (99:1). Indeed, dams administered the dose level of 3 mg/kg bw/d from GD6 to PND10 showed decreased motor activity, hunched posture, head tilt or lost righting reflex during gestation and ataxia or abnormal autonomic function during the lactation period. Mortality was also reported in three of the dams showing clinical signs of neurotoxicity on gestation days 19-20 and lactation day 3. As no neurotoxic effects were observed in rats during other repeated-dose studies, it could be argued that the dams seem to be more susceptible to neurotoxic effects induced by DPX-KN128 (99:1) than non-pregnant females. Nevertheless, such clinical signs were not reproduced in the prenatal developmental rat toxicity study with DPX-KN128 (99:1) at the same range of dose levels. It is to note that the highest tested dose levels in rats in other repeated-dose studies (up to approx. 15 mg/kg bw/d) were below the dose levels leading to neurotoxic effects in the mouse studies and in the acute rat neurotoxicity study. Moreover, specific neurofunctional testing was not performed in all available rat studies.

The systemic NOAELs of the acute and 90-d neurotoxicity studies were based on decreased body weights, body weight gains and food consumption observed at the LOAEL. It is noted that no haematology measurement was perfomed in the 90-day study, whereas other studies have indicated the occurrence of effects on red blood cell parameters to be critical. Mortality was reported in 3 out of 12 female rats in the subchronic neurotoxicity study on test days 9 to 12.

In the newly submitted developmental neurotoxicity study, the offspring NOAEL is 1.5 mg/kg bw/day based on increased number of stillborn pups, increased pup mortality on PND1 to 4 and decreased pup weight per litter on PND0 at the dose level of 3 mg/kg bw/day. Rat offsprings were not more susceptible to potential neurotoxicity effects of indoxacarb based on the absence of neurobehavioral effects at the highest dosage tested of 3 mg/kg/day. The maternal NOAEL is set at 1 mg/kg bw/d based on decreased body weight gains observed during gestation at the dose level of 1.5 mg/kg bw/d.

2.6.8. Summary of further toxicological studies on the active substance

Supplementary studies on the active substance:

Distribution of the radioactivity in erythrocytes of rats administered a single oral dose of 111-113 mg/kg bw DPX-JW062 (50:50) by gavage showed that the major identified compound was IN-P0036.

In a 28-day immunotoxicity study in mice, DPX-KN128 (99:1) was not shown to induce adverse effect on the humoral immune response.

Table 2.6.8-1
Summary of supplementary studies on indoxacarb (DPX-KN128 and DPX-JW062)

Type of study and test substance	Doses/ concentrations tested	NOAEL	LOAEL	Target organ(s) and/or effects	Reference
Distribution of erythrocytes (Gavage) Rat DPX-JW062 (50:50)	M: 111-113 mg/kg bw Single dose	Not applicable	Not applicable	IN-P0036 was the single radioactive species associated with erythrocytes 72-h after administration	[redacted] 1999 DuPont-1952
28-day immunotoxicity (Feeding), Mouse DPX-KN128 (99:1)	F: 0, 10, 25, 10, 100 ppm – 0, 2, 5, 11, 23 mg/kg bw/d	Immunotoxicity: 100 ppm 23 mg/kg bw/d Systemic: 100 ppm 23 mg/kg bw/d	Immunotoxicity: >100 ppm >23 mg/kg bw/d Systemic: >100 ppm >23 mg/kg bw/d	Immunotoxicity: no effect on the humoral immune response Systemic: no effect	[redacted] 2011 DuPont-29280*

* Studies newly submitted

Postulated mode of action of indoxacarb:

The racemic mixture DPX-JW062, the 75:25 S:R enantiomeric blend DPX-MP062 and the pure S-enantiomer DPX-KN128 induced effects on red blood cell parameters and histopathological findings in the spleen, the bone marrow, the liver and/or the kidney in short-term and long-term toxicity studies in all tested species.

In rats, as demonstrated in ADME studies with DPX-MP062 (75:25) and DPX-JW062 (50:50), one of the metabolic pathways involved the opening of the oxadiazine ring and subsequent cleavages, resulted in the formation of aniline analogs metabolites. Aniline and related compounds are well-known to be responsible of haemolytic anemia with associated changes in spleen, bone marrow and liver of rats.

In particular, indoxacarb is metabolised to an arylamine metabolite IN-P0036 (4-trifluoromethoxyaniline). This metabolite is found at low level in the rat urine but is an intermediate in the metabolic pathway leading to the formation of 2 major urine metabolites (MC218 representing 21-24% of the administered dose and MG195 representing 14-17% of the administered dose after DPX-JW062 (50:50) administration). IN-P0036 was also shown to be associated with erythrocytes following administration of DPX-JW062 (50:50) in rats. The haemolytic potential of this metabolite was not investigated in further studies.

Nevertheless, according to the applicant, the mechanism of arylamine-induced oxidant effects on red cells has been determined for a number of compounds in this class and is dependent upon biotransformation of the arylamine to its N-hydroxylamine. Therefore, the haemolytic potential of IN-MT713, the N-hydroxy derivative of 4-trifluoromethoxyaniline, although not detected in the rat metabolism, has been investigated. IN-MT713 had a dose-dependent *in vitro* haemolytic potential, determined as glutathione oxidation, in erythrocytes of rats, dogs and humans.

Therefore, according to this postulated mode of action, indoxacarb-induced haematologic effects are indirect, requiring conversion of the parent molecule to IN-P0036 and subsequent conversion of that metabolite to its hydroxylamine IN-MT713.

According to the applicant, it is interesting to note that the arylamine metabolite, produced from the trifluoromethoxyphenyl portion of the parent compound, does not contain the chiral center of the molecule. Therefore, if haematological effects observed after administration of indoxacarb are related to the formation of this metabolite, it could be expected that haematological effects produced following exposure to either the racemic, the 75:25 enantiomer blend or the pure S-enantiomer would

be similar irrespective of the isomeric blend. This assumption is also supported by the results of a regression analysis of changes in red cell mass parameters following subchronic dietary exposure to the 3 compounds.

The RMS FR considered that indoxacarb could produce haematological effects *via* this postulated mode of action although some uncertainties remained (e. g. IN-MT713 was not detected in the rat metabolism, conversion of IN-P0036 to IN-MT713 was not demonstrated). Moreover, it cannot be excluded that the formation of this aniline metabolite could be influenced by the ratio of isomers. As an example, as shown in the ADME studies, the S-isomer DPX-KN128 was found to be the preferred substrate for the enzymatic reaction leading to the formation of the metabolite IN-JT333. Therefore, given the uncertainties in the enzymatic reaction, the speculated absence of difference of toxicity due to the formation of a non-chiral metabolite is questionable. However, according to the results of the three available 90-day toxicity studies in rats, it was shown that the NOAELs/LOAELs of the three enantiomeric blends (ratios of approx. 99:1, 75:25 and 50:50 of isomers S and R respectively) were similar *in vivo*.

Endocrine disruption potential:

No histopathological effects were observed on endocrine-related tissues in the repeated-dose toxicity studies with DPX-JW062 (50:50), DPX-MP062 (75:25), or DPX-KN128 (99:1). In addition, no effects on reproduction were observed in the multigeneration reproduction study conducted with DPX-JW062 (50:50), in the developmental studies in rats with DPX-JW062 (50:50), DPX-MP062 (75:25), and DPX-KN128 (99:1), or the developmental neurotoxicity study with DPX-KN128 (99:1).

Two publications dealing with potential ED effects of several substances, including indoxacarb, were retrieved after the literature review. These publications were provided and considered relevant and reliable by the applicant (but no summary was submitted).

- In a publication by Orton *et al.* (2011), indoxacarb (racemic form was not specified in the publication) was tested in the MDA-kb2 assay for potential androgen activity. There were no effects at a cytotoxic concentration of 11.3 µM.

- In a publication by Sipes *et al.* (2013), indoxacarb was tested in a battery of assays used for the U.S. Environmental Protection Agency ToxCast Program. This publication only presented the test results for compounds which were positive in the suite of assays. The results for indoxacarb were not discussed in the manuscript, indicating that positive responses were not obtained for indoxacarb.

Therefore, in the absence of effects which could be mediated by an ED mode of action in apical studies and in the absence of relevant effects in literature review, additional studies for potential endocrine effects are not warranted.

2.6.9. Summary of toxicological data on impurities and metabolites

Metabolites:

Summary data for IN-KG433:

The oral LD_{50} of IN-KG433 was estimated to be 174 mg/kg bw in female rats.
IN-KG433 is negative in an Ames test and in an *in vitro* gene mutation assay in mammalian cells. An *in vitro* UDS assay was performed in mammalian cells, nevertheless, this test is not considered sensitive enough and the OECD test guideline 482 was deleted in April 2014.
An *in vitro* chromosomal aberration assay is lacking for this metabolite to assess its genotoxic potential. Nevertheless, IN-KG433 is not a metabolite found in groundwater or in residues at

significant level. Therefore, this test is not considered needed in the context of the renewal of approval of the active substance.

Table 2.6.9-1
Summary of toxicity data for IN-KG433

Type of study	Test conditions	Results	Reference
IN-KG433			
Oral LD50	Rat Males: 5000 mg/kg bw Females: 250, 500, 2000 mg/kg bw	M: LD50 > 5000 mg/kg bw F: LD50 = 174 mg/kg bw	[redacted] 1997 HLO-1997-00469
Ames test	*Salmonella typhimurium* strains TA98, TA100, TA1535, and TA97a *Escherichia coli* strain WP2 uvrA (pKM101) Up to 5000 µg/plate in the presence and absence of S9 activation	Negative	Wagner and Reece 1997 HLO-1997-00254
In vitro gene mutation assay in mammalian cells	Chinese Hamster Ovary cells (CHO K1 BH4) Locus HGPRT Up to 5000 µg/mL in the presence and absence of S9 activation	Negative	San and Clarke 1997 HLO-1997-00405
In vitro UDS assay in mammalian cells	Primary rat hepatocytes Up to 1000 µg/mL	Negative	San and Sly 1997 HLO-1997-00406

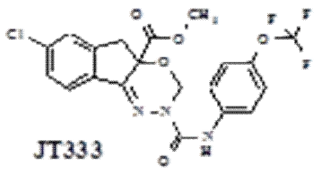
Summary data for IN-JT333:
The oral LD_{50} of IN-JT333 was estimated to be 39 mg/kg bw in female rats.
IN-JT333 is negative in an Ames test, in an *in vitro* gene mutation assay in mammalian cells and in an *in vitro* chromosomal aberration assay. It can thus be concluded that IN-JT333 is not an *in vitro* genotoxicant.
A 14-day oral toxicity study with IN-JT333 is available in the rats. Nevertheless, this test being not GLP and not OECD guideline compliant and showing some deficiencies in its protocol (e.g. haematological parameters, clinical chemistry, and histopathology were not performed), comparison of the toxicity profile to that of the active substance indoxacarb is not possible.

Table 2.6.9-2
Summary of toxicity data for IN-JT333

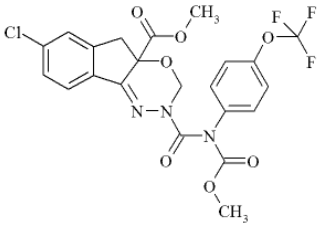
Type of study	Test conditions	Results	Reference
IN-JT333			
Oral LD50	Rat Males and females 10, 30, 50, 100 and 200 mg/kg bw	M: LD50 = 52 mg/kg bw F: LD50 = 39 mg/kg bw	[redacted] 1996 HLR 927-96
Ames test	*Salmonella typhimurium* strains TA98, TA100, TA1535, and TA97a *Escherichia coli* strain WP2 uvrA (pKM101) Up to 5000 µg/plate in the presence and absence of S9 activation	Negative	Mathison 1996 HLR 830-96
In vitro gene mutation assay in mammalian cells	Chinese Hamster Ovary cells (CHO K1 BH4) Locus HGPRT Up to 125 µg/mL in the presence and absence of S9 activation	Negative	San and Clarke 1997 HLO 925-96
In vitro chromosome aberrations assay	Human peripheral blood lymphocytes Up to 2000 µg/mL	Negative	Gudi and Schadley 1996 HLO 951-96
14-day oral study	Rat Feeding 0, 2, 10, 40, 100 ppm Males: 0.19, 0.88, 3.0, 5.6 mg/kg bw/d Females: 0.18, 0.87, 2.9, 4.5 mg/kg bw/d	*Study not considered acceptable*	[redacted] 1992 HLR 475-91

IN-JT333 is a residue metabolite. Therefore, this metabolite should be assessed in order to compare its toxicity to the toxicity of the parent compound.

The chemical structures of each compound are shown below.



IN-JT333



Indoxacarb

IN-JT333 is not genotoxic *in vitro*. IN-JT333 is more acutely toxic than indoxacarb with a LD_{50} of 39 mg/kg bw in females (LD_{50} are equal to 179 mg/kg bw and 268 mg/kg bw for DPX-KN128 (99:1) and DPX-MP062 (75:25) respectively). No acceptable repeated-dose toxicity study is available with IN-JT333 to compare the respective toxicities of IN-JT333 and indoxacarb.

As described in B.6.1, DPX-MP062 (75:25) and DPX-JW062 (50:50) are extensively metabolized in male and female rats, with the predominant distribution of total radioactivity to the fat for both DPX-MP062 (75:25) and DPX-JW062 (50:50). IN-JT333 was the most important metabolite found in fat, representing approximately >95% of the total radioactive residue in that compartment in females following a single oral dose of 5 mg/kg DPX-JW062 (50:50) or DPX-MP062 (75:25).

Table 2.6.9-3
Percentage (%) of total administered dose in male and female rats administered a dosage of 5 mg/kg/bw/day of indoxacarb

	Males DPX-JW062 (50:50)	**Female DPX-JW062 (50:50)**	**Male DPX-MP062 (75:25)**	**Female DPX-MP062 (75:25)**
Total tissue residue	3.4	7.8	4.4	12.9
Total Fat residue	1.76	4.7	2.6	8.76
Total IN-JT333 residue in fat (% total radioactive residue in fat)	92 *n=1*	96-99.5 mean = 98.2 *n=5*	93 *n=1*	91.5-98.4 mean = 96.4 *n=5*

In females, which is the most sensitive sex following administration of indoxacarb or IN-JT333 (as determined in the acute oral study), IN-JT333 is present at approx. 4.6% in the fat following administration of DPX-JW062 (50:50) ((4.7*98.2)/100) and 8.5% in the fat following administration of DPX-MP062 (75:25) ((8.8*96.4)/100). As described in B.6.1, DPX-KN128 (99:1) was shown to be the preferred substrate for the enzymatic removal of the N-carboxymethyl group in the parent compound, leading to the formation of the metabolite IN-JT333. Therefore, it can be expected that a greater amount of IN-JT333 would be present in the fat of rats administered the pure S-enantiomer DPX-KN128.

Nevertheless, IN-JT333 was not found in the urine of rats and the quantity of this metabolite sequestered in the fat would not be bioavailable.

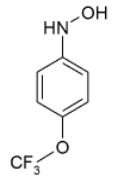
Overall, a short-term repeated dose toxicity study is considered useful to compare the toxicity of the active substance and this residue metabolite and to set reference values for this compound.

At a late stage during the assessment of the active substance, the applicant agreed with the RMS to conduct a guideline repeated-dose toxicity study with IN-JT333 and proposed to perform a 28-day study (OECD 407).

Meanwhile, as a worst-case approach, it is proposed to use the TTC approach. IN-JT333 is not genotoxic in *in vitro* genotoxicity studies. Therefore, the TTC value for non-genotoxic Cramer class III substances can be used: 0.0015 mg/kg bw/d.

Summary data for IN-MT713:

The chemical structure of IN-MT713 (N-hydroxy-4-trifluoromethoxyaniline) is as follows:



IN-MT713

IN-MT713 (N-hydroxy-4-trifluoromethoxyaniline) was not found in the rat after administration of indoxacarb. On the contrary, 4-trifluoromethoxyaniline (IN-P0036) was found to be associated with erythrocytes of rats following administration of indoxacarb. According to the study authors, by analogy to other haemolytic arylamines, which need to be converted to their N-hydroxylated metabolites to exert their haemolytic activity, IN-MT713 is thought to be the metabolite ultimately responsible for indoxacarb-induced haemolytic effects.
IN-MT713 had a dose-dependent haemolytic potential *in vitro* in erythrocytes of rats, dogs and humans, demonstrated by the oxidative effect on glutathione in erythrocytes. Based on the *in vitro* results, humans are likely to be less sensitive to the haemolytic effects of the metabolite than rats or dogs. Furthermore, the *in vitro* haemolytic potential of IN-MT713 was investigated in erythrocytes of glucose-6-phosphate dehydrogenase (G6PDH) normal and deficient humans. G6PDH-deficient individuals may be slightly more sensitive to the oxidative effects of the metabolite than G6PDH-normal individuals.
Nevertheless, based on these results, it cannot be stated with certainty that humans would be less sensitive to haemolysis induced *in vivo* after administration of indoxacarb. Indeed, the mode of action of indoxacarb is not clearly established (see B.6.8.2). Furthermore, in contrast, published data showed than dogs and humans are more sentitive than rats to e.g. the formation of MetHb[2], which was demonstrated to occur in the only 90-d rat study where this parameter was measured.

<u>Impurities:</u>

Specifications were set for four relevant impurities in DPX-KN128 technical: impurity IN-06439 or tetraethyl base (<2.5ppm), impurity IN-R1T94 or tetraethyl hydrol (<2.5 ppm), impurity IN-C0800 or tetraethyl ketone (<2.5ppm) and impurity IN-J1063 or Ethyl violet (<1.8ppm).

[2] Muller et al. 2006 – Hazard classification of chemicals inducing haemolytic anemia: an EU regulatory perspective. Regulatory Toxicology and Pharmacology 45 (2006) 229-241

Regarding the structure formula of these compounds and the results of (Q)SAR and read-across analysis these four impurities have to be considered as genotoxic carcinogens. The approach used to determine if the proposed specifications of these relevant impurities are appropriate is in accordance with *EFSA Scientific Opinion on the applicability of the Margin of Exposure approach for the safety assessment of impurities which are both genotoxic and carcinogenic in substances added to food/feed* (EFSA Journal 2012; 10(3):2578). BMDL10 were calculated from animal studies performed on structurally similar compounds. The assessment showed Margin of Exposure (MOE) greater than 10000 for each impurity and for the sum of the four impurities (cumulative risk assessment justified by the structural similarities of these four compounds). According to EFSA Scientific Opinion (2012), the magnitude of the calculated MOE would be of low concern from a public health point of view.

Results of (Q)SAR and read-across analysis, literature review conducted on the relevant impurities and on their structurally similar compounds, available toxicity studies performed on the analogues of these impurities as well as the MOE approach are included in Volume 4.

2.6.10. Summary of medical data and information

Indoxacarb (DPX-KN128) technical and its end use products are produced on a commercial scale. No illnesses have been attributed to exposure associated with the handling, testing, or manufacturing of indoxacarb (DPX-KN128) technical or its end use products at the facilities where the technical material is manufactured or formulated into the end use products.

Five published reports of clinical cases and poisoning incidents linked to indoxacarb use were reported. In all 5 cases, increased methemoglobin and secondary clinical signs improved following gastric lavage, activated charcoal, intravenous fluid, oxygen/mechanical ventilation, intravenous treatment with methylene blue and, in some cases, Vitamin C. In addition, symptoms of kidney effects were treated with continued fluids, sodium bicarbonate, and/or continuous ventilation, and other supportive measures. In all 5 cases, the patients recovered.

There have been no epidemiological studies conducted with indoxacarb (DPX-KN128). Although there have been 5 incidences of over-exposure to indoxacarb since the beginning of commercial use, there are no reports of adverse effects on human health following standard use as described on the product label or from handling the technical material or formulated product during manufacturing.

2.6.11. Toxicological end point for assessment of risk following long-term dietary exposure - ADI

During the first EU approval of indoxacarb, the ADI was set at 0.006 mg/kg bw/d, based on an overall NOAEL of 0.6 mg/kg bw/d for short- and long-term exposure in rats and by using a safety factor of 100 (Review Report SANCO/1408-2001 rev.3, 23 september 2005).

The following justification was agreed:
"Since it was convincingly demonstrated by the notifier that the critical effects (i.e. the effects on red blood cell parameters) are not a function of the chiral portion of the molecule, but rather of the arylamine metabolite P0036, the available NOAELs/LOAELs for the different isomeric mixtures can be used for the risk assessment without further correction for differences in DPX-KN128 content.
In the evaluation of the effects on circulating red blood cells in the individual studies, a slight but significant decrease in one of the parameters of circulating erythrocyte numbers (RBC count, Hb, Ht) was considered as adverse. It is however recognized that a very slight but significant deviation in one circulating red blood cell parameter, in the absence of other effects (increased haemosiderin pigment

in liver, kidneys, spleen and bone marrow, presence of Heinz bodies and met-Hb, increased serum bilirubin values, absence of regenerative responses (increased MCV and reticulocyte counts, extramedullary haemopoiesis and mixed cell hyperplasia in bone marrow)), is likely to be fortuitous. Furthermore, dose-dependency naturally plays an important role in assessing the adversity of the effects. Unfortunately, in the available studies the existence of a dose-response relationship was obscured by the small differences in the dose levels.
Keeping this in mind and comparing all available data with DPX-MP062 (enriched isomer mixture) and DPX-JW062 (racemic mixture), it is concluded that the overall NOAEL for DPX-MP062 for short- and long-term exposure would be 10 ppm for male and female rats, equivalent to 0.6 mg/kg bw. This 'overall NOAEL' for DPX-MP062 of 0.6 mg/kg bw is used to derive the AOEL and ADI."

Based on the same toxicological database, an ADI of 0.01 mg/kg bw/d was set by the JMPR (2005). In view of these discrepancies, the Commission requested the RMS NL to write an addendum to re-evaluate the derivation of the ADI. In this post-approval addendum, available in 2007, some of the critical studies were re-assessed by the RMS NL based on a slightly different evaluation of the adversity of haematological effects (see 2.6.3). The RMS NL came to the following conclusion:
"In the above performed re-evaluation of the relevant studies, only the NOAEL of the 2-year rat study has been changed (from 0.55 to 1.04 mg/kg bw/day). This study could be used as the basis to derive the ADI. There are however, short-term NOAELs which are lower than 1.04 mg/kg bw/day. It is important to note that the dose-response curve for indoxacarb is very shallow and that makes it difficult to select the most suitable NOAEL. Although the NOAEL of one 90-d rat study ([redacted] 1997) is lower than 1 mg/kg bw/day (the NOAEL was set at <0.76 mg/kg bw/day), the NOAEL of the other 90-day study in rats ([redacted] 1997b) is 0.99 mg/kg bw/day. Also the NOAELs in the dog studies are lower than 1 mg/kg bw/day. It should however be noted that, although the above re-evaluation is less conservative than the EU-DAR, the effects at the LOAEL are still relatively marginal effects.
The difficulty of this discussion, which effects are adverse and which not, is illustrated by the EU-evaluation process of indoxacarb:
The DAR was conservative and used as a starting point. The subsequent discussion in the EU was however inconclusive and therefore, the SCP was asked for advice. Also the SCP concluded that dose-response curves were always very shallow and that a clear NOAEL could not be identified. The SCP came, after consideration of all relevant knowledge, to the conclusion that the overall NOAEL was 2.4 mg/kg bw/day. A few Member States did not accept the SCP opinion and argued for a more conservative evaluation.
In conclusion, it is very difficult to identify a clear NOAEL, because of the very shallow dose-response curve and the difficult discussion which effects are adverse and which not. The overall NOAEL will be around 1 mg/kg bw/day, based on the 90-day rat study and the 2-year rat study, supported by the reproduction and teratogenicity studies, and taking into account that the effects observed at the LOAEL in the other 90-day rat study, and the two dog studies, are relatively marginal effects."

Given the similarities of the results of the three 90-day studies performed with the three forms of indoxacarb (containing isomers DPX-KN128 and IN-KN127 in a ratio of 90.4:0.6, 75:25 or 50:50), the available NOAELs/LOAELs for the different isomeric mixtures can be used for the risk assessment without further correction for differences in DPX-KN128 content.

The NOAELs of the 90-day rat studies performed either on DPX-KN128 (99:1), DPX-MP062 (75:25) or DPX-JW062 (50:50) ranged from approximately 0.6 to 1 mg/kg bw/d, with LOAELs from 0.8 to 3.2 mg/kg bw/d based on haemolytic effects.
In dogs, no NOAELs can be identified and the LOAELs were equal to 1 mg/kg bw/d and 1.1 mg/kg bw/d in the 90-day and 1-year dog studies respectively, based on haemolytic effects.
The NOAEL of the long-term toxicity study was 1.04 mg/kg bw/d and the LOAEL, based on haemolytic effects, was 2.13 mg/kg bw/d in the most sensitive species, i.e. the rat.

Relevant NOAELs were also reported in other studies, in which the haematological effects were not determined. Particularly, both the parental and offspring NOAELs of the 2-generation study were 1.2

mg/kg bw/d and the LOAELs were 3.7 mg/kg bw/d. In addition, in the subchronic neurotoxicity study in rats, the systemic NOAEL was 0.685 mg/kg bw/d and the LOAEL was 3.3 mg/kg bw/d in females.

For the renewal of the active substance, the same short- and long-term toxicological studies were available. In addition, amongst the new studies submitted for the purpose of the renewal, two critical studies were identified: a developmental toxicity study and a developmental neurotoxicity study performed in rats on DPX-KN128 (99:1).
Indeed, in the developmental rat toxicity study conducted with the S-enantiomer DPX-KN128 (99:1), the maternal NOAEL is set at 0.5 mg/kg bw/d based on the decreased body weight gains observed from the LOAEL of 1 mg/kg bw/d. In the developmental neurotoxicity study, the maternal NOAEL is 1 mg/kg bw/d, based on decreased body weight gains at the dose level of 1.5 mg/kg bw/d.

Therefore, based on the complete dataset, the RMS FR did not consider acceptable to determine an overall NOAEL of 1 mg/kg bw/d for setting the toxicological reference values. Indeed, adverse effects were observed at this dose level and even below in some studies:
- In the dog studies, no NOAEL was determined. The LOAELs were equal to 1 mg/kg bw/d and 1.1 mg/kg bw/d in the 90-day and 1-year dog studies respectively. At these dose levels, decreased haemoglobin, haematocrit and red blood cell count of greater than 10% were observed, as well as associated histopathological findings in several organs: increased pigment in the liver, kidney, spleen and/or bone marrow, hyperplasia in the bone marrow and extramedullary haematopoiesis in the spleen. These effects should be considered adverse. Based on these results, it cannot be speculated that the dog is less sensitive than the rat to the haemolytic effects induced by indoxacarb.
- In the 90-day rat studies, the NOAELs were in general lower than 1 mg/kg bw/d with LOAELs greater than 1 mg/kg bw/d, except in females administered DPX-MP062 (75:25) for which no NOAEL was identified and the LOAEL was <1 mg/kg bw/d (= 0.76 mg/kg bw/d).
- In the newly submitted developmental rat toxicity study, decreased maternal body weight gains were observed from the dose level of 1 mg/kg bw/d, the NOAEL of this study being equal to 0.5 mg/kg bw/d.

As a conclusion, the RMS FR proposal is to set an **ADI of 0.005 mg/kg bw/d**, based on the maternal NOAEL of 0.5 mg/kg bw/d determined in the developmental rat toxicity study performed with DPX-KN128 and applying a safety factor of 100. This value is supported by the results of the short- and long-term toxicity studies in rats and dogs.

Due to the small dose spacing, the margin of safety between the LOAEL of the developmental rat toxicity study and the ADI is also equal to 200, which is considered acceptable for an effect on the body weight gains of pregnant rats. Moreover, although no NOAEL was established in dogs in the 90-day and 1-year studies, the margin of safety between the LOAEL and the proposed ADI is equal to 200, which is considered sufficient in view of the nature of the effects observed at the LOAEL. It should also be noted that criteria set to determine the NOAEL are very conservative in regards to haematological effects.

2.6.12. Toxicological end point for assessment of risk following acute dietary exposure - ARfD (acute reference dose)

During the first EU approval of indoxacarb, the ARfD was set at 0.125 mg/kg bw/d, based on the NOAEL of 12.5 mg/kg bw/d determined in the acute neurotoxicity study in rats and by using a safety factor of 100 (Review Report SANCO/1408-2001 rev.3, 23 september 2005).

In the newly submitted developmental rat toxicity study performed on DPX-KN128 (99:1), decreased maternal body weight gains were observed from the dose level of 1 mg/kg bw/d, the NOAEL of this study being equal to 0.5 mg/kg bw/d. As this effect occurred from the beginning of the treatment (-

62% decrease compared to the control group on GD 6-8), it is considered relevant for the setting of the ARfD.

Therefore, using a safety factor of 100, the **ARfD is set at 0.005 mg/kg bw/d.**

2.6.13. Toxicological end point for assessment of occupational, bystander and residents risks – AOEL

During the first EU approval of indoxacarb, the AOEL was set at 0.004 mg/kg bw/d, based on an overall NOAEL of 0.6 mg/kg bw/d for short- and long-term exposure in rats and by using a safety factor of 100 and a factor of 0.60 for incomplete oral absorption (Review Report SANCO/1408-2001 rev.3, 23 september 2005).

Based on the argumentation developed in 2.6.11, the AOEL is derived on the same basis as the ADI.

Therefore, an **AOEL of 0.003 mg/kg bw/d** is proposed, based on the maternal NOAEL of 0.5 mg/kg bw/d determined in the developmental rat toxicity study performed with DPX-KN128 (99:1), applying a safety factor of 100 and taking into account an oral absorption of 60%. This is supported by the results of the short-term toxicity studies in rats and dogs.

An acute AOEL is also proposed for indoxacarb. An **AAOEL of 0.003 mg/kg bw/d**, derived on the same basis as the ARfD and taking into account an oral absorption of 60%, is proposed.

2.6.14. Summary of product exposure and risk assessment

The representative formulation for renewal of approval of indoxacarb is Indoxacarb 150 g/L EC, an emulsifiable concentrate (EC) formulation containing 150 g/L indoxacarb.

Acute toxicity:
Acute toxicity studies were conducted with Indoxacarb 150 g/L EC. Summaries of these studies are presented below.

Table 2.6.14-1
Summary of acute toxicity data for Indoxacarb 150 g/L EC

Type of study	Species	Results	References
Acute oral LD_{50}	Rat	LD_{50} = 976.8 mg/kg	[redacted] 2004 DuPont-13455
Acute dermal LD_{50}	Rat	LD_{50} >5000 mg/kg	[redacted] 2003 DuPont 13456
Acute inhalation LC_{50} (4 h)	Rat	LC_{50} >5.2 mg/L	[redacted] 2004 DuPont 13460
Skin irritation	Rabbit	Not irritating	[redacted] 2003 DuPont 13457
Eye irritation	Rabbit	Not irritating	[redacted] 2003 DuPont-13459
Skin sensitisation (Maximisation)	Guinea Pig	Not sensitising	[redacted] 2003 DuPont-13458

Indoxacarb 150 g/L EC had no significant toxicity by the dermal or inhalation routes of exposure. It was harmful by the oral route of exposure. Indoxacarb 150 g/L EC is not an eye or skin irritant and does not cause skin sensitisation.

Supplementary studies on the plant protection product:
A 28-day and a 90-day rat toxicity studies were carried out with the formulation Indoxacarb 150 g/L EC. The NOAEL of the 90-day toxicity study, performed in female rats only, is set at 62.5 ppm (3.82 mg/kg bw/d) of Indoxacarb 150 g/L EC, based on decreased body weights, body weight gains and food consumption, as well as findings related to haemolytic anemia (decreased red blood cell parameters and increased reticulocytes, as well as haemosiderin deposits in the spleen of 40% of the tested rats) at the dose level of 125 ppm (7.53 mg/kg bw/d) of Indoxacarb 150 g/L EC.

Classification for human health:
Taking into account the results of toxicity studies performed on the representative formulation and the classification of the active substance and co-formulants, Indoxacarb 150 g/L EC should be classified as Category 4 for acute oral toxicity (H302) and Category 1 for Specific Target Organ Toxicity following Repeated Exposure (STOT-RE) (H372) according to the provisions of Regulation (EC) No. 1272/2008.

Dermal absorption:
The dermal absorption of indoxacarb from Indoxacarb 150 g/L EC was investigated *in vivo* in the rat and *in vitro* using both rat and human skin. Using the triple pack approach, the following dermal absorption values have been used for risk assessments:

- 2% for the concentrate
- 18% for field dilutions

Operator:
According to the German model, for tractor mounted boom sprayer application in field, there is no unacceptable risk anticipated for operator wearing PPE.
For information, according to EFSA calculator[3], there is no unacceptable longer term risk anticipated for operator wearing PPE whereas the acute risk assessment showed exposure greater than the proposed AAOEL even with the use of PPE.

Bystander:
For all the intended uses, there is no unacceptable risk anticipated for a bystander incidentally exposed to Indoxacarb 150 g/L EC.
For information, according to EFSA calculator, there is no unacceptable risk anticipated for an adult bystander incidentally exposed to Indoxacarb 150 g/L EC, whereas an unacceptable risk is anticipated for a child.

Resident:
For all the intended uses, there is no unacceptable risk anticipated for a resident exposed to Indoxacarb 150 g/L EC.
For information, according to EFSA calculator, there is no unacceptable risk anticipated for an adult resident exposed to Indoxacarb 150 g/L EC, whereas an unacceptable risk is anticipated for a child.

Worker:
For maize, there is no unacceptable risk anticipated for the worker wearing PPE.
For lettuce, there is no unacceptable risk anticipated for the worker wearing PPE when re-entering crops treated once or twice with Indoxacarb 150 g/L EC. Nevertheless, in case of 4 applications on lettuce as proposed by the applicant, an unacceptable risk is anticipated for the worker even with the use of PPE.

[3] Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874

For information, according to EFSA calculator, there is no unacceptable risk anticipated for worker wearing work wear when re-entering maize crops, whereas an unacceptable risk is anticipated for worker wearing PPE when re-entering lettuce crops.

As a conclusion, according to current used models, there is no unacceptable risk anticipated for the operator wearing PPE, the bystander and the resident for all of the intended uses of Indoxacarb 150 g/L EC.
Furthermore, no unacceptable risk is anticipated for the worker wearing PPE for maize. For lettuce, no unacceptable risk is anticipated for the worker wearing PPE if the maximum number of application is 2. In case of 4 applications on lettuce, as proposed by the applicant in the GAP table, an unacceptable risk is anticipated for the worker even with the use of PPE.

2.7. RESIDUE

2.7.1. Summary of storage stability of residues

Storage stability of indoxacarb (DPX-KN128/DPX-KN127) has been investigated in apples, grapes, tomatoes, lettuce and maize grain and silage. Stability of DPX-KN128/IN-KN127 and its five metabolites (IN-KB687, IN-KG433, IN-KT319, IN-JU873 and IN-JT333) was investigated in hen-derived matrice (whole eggs, muscle, fat and liver). Summary of storage stability data submitted in the framework of initial DAR and in the framework of the renewal are reported in the following table.

Plant products (Category)	**Active ingredient**	**Commodity**	**T** (°C)	**Stability** (Months)
High water content	DPX-KN128/DPX-KN127	Apples	-20°C	18
High water content		Apple juice	-20°C	6
High acid content		Grapes	-20°C	18
High acid content		wine	-20 °C	3
High water content		Tomatoes	-20°C	12
High water content		Lettuce	-20°C	11
High starch content		Maize grain	- 20°C	13
Hen matrice	DPX-KN128/DPX-KN127, IN-KB687, IN-KG433, IN-KT319, IN-JU873 and IN-JT333	Whole eggs (hen)	- 20°C	16
		Muscle (hen)	- 20°C	16
		Fat (hen)	- 20°C	16
		Liver (hen)	- 20°C	16

From the available data, it can be concluded that indoxacarb (DPX-KN128/DPX-KN127) is stable under deep frozen conditions for a period of 18 months in commodities with high water (apples) and high acid (grapes) content, for a period of 13 months in high starch content and for a period of 16 months in hen-derived matrices.

In submitted trials, samples of interest have been stored in compliance with the available storage stability data.

2.7.2. Summary of metabolism, distribution and expression of residues in plants, poultry, lactating ruminants, pigs and fish

Plant metabolism studies

Metabolism of indoxacarb was investigated for foliar application on fruits and fruiting vegetables (grapes, tomatoes), on leafy vegetables (lettuce) and on pulses and oilseeds (cotton), using indanone labelled and trifluoromethoxyphenyl ring labelled DPX-JW062 (a racemic mixture 50:50 mixture of the insecticidally active enantiomer DPX-KN128 and the inactive enantiomer IN-KN127). The characteristics of the study are summarized in the table below.

Summary of available metabolism studies in plants

Group	Crop	Label position	Type/(F) or (G) or (I)	Application details			
				Rate	No	Sampling	Remarks
Fruits and fruiting vegetable	Grape	indanone-1-^{14}C or trifluoromethoxy-phenyl ring -^{14}C	Foliar application (F)	500 g/ha, (equal to 250 g DPX-KN128/ha) (a)	1	DAT 0, 14, 46, and 66 for grapes 0, 7, 14, 31, 46, and 66 for leaves	-
	Tomato	trifluoromethoxy-phenyl ring-^{14}C radiolabelled	Foliar application (n.r.)	150 g/ha, (equal to 75 g DPX-KN128/ha) (a)	4 (6-10 days between)	DAT 0 (leaf), 3, 7, and 14 days (leaf and fruits)	-
Leafy vegetables	Lettuce	indanone-1-^{14}C or trifluoromethoxy-phenyl ring -^{14}C	Foliar application (n.r.)	500 g as/ha, (equal to ca. 250 g DPX-KN128/ha) (a)	1	DAT 0, 7, 14, 21, 28, and 35 days (plant samples)	-
		Trifluoromethoxy-phenyl ring-^{14}C radiolabelled	Foliar application (n.r.)	625 g DPX-JW062/ha, (equal to ca. 313 g DPX-KN128/ha) (a)	4 (7 days between)	DAT 0, 7, 14, 21 and 28 days (plant samples)	-

Group	Crop	Label position	Type/(F) or (G) or (I)	Application details			
				Rate	No	Sampling	Remarks
Pulses and oilseeds	Cotton	indanone-1-^{14}C[IND], and trifluoromethoxy-phenyl ring-^{14}C[TMP]	Foliar application (F)	500 g /ha, (equal to 250 g DPX-KN128/ha) (a)	1	DAT 0, 7, 14, 30, 59, and 90 days (plant samples)	-
		indanone-1-^{14}C or trifluoromethoxy-phenyl ring -^{14}C	Foliar application (F)	625 g/ha, (equal to 313 g DPX-KN128/ha) (a)	4 (10 days between)	DAT 0, 9, 20, 30 days, and maturity (plant samples)	-

r.: not reported
(a): DPX-KN128 is the *S* enantiomer of indoxacarb

In all crops, metabolism studies indicated that DPX-JW062 isomers (DPX-KN128 and IN-KN127) represent the major residue components (accounting for 60 – 94% of the TRR). Other residue components were detected only in very small amounts and were not identified. Since DPX-KN128 and IN-KN127isomers were found following chiral analysis in similar amounts, it was concluded that plant metabolism of indoxacarb is not stereo specific. Also considering that toxicity was assessed with mixture of isomers, the ratio of both isomers used in different metabolism studies and residue trials is not considered to be of concern. Consequently, the residue definition for enforcement and risk assessment in all plant commodities was defined as the sum of indoxacarb (DPX-KN128) and its R enantiomer (IN-KN127). Validated analytical methods for enforcement of the proposed residue definition are available except for dry commodities. Considering that the use of indoxacarb is also supported in maize, an analytical method for enforcement of the proposed residue definition in dry commodities is still required.

Two additional metabolism studies performed on cotton and lettuce have been disregarded since unsufficient technical details were available in the study reports.

Livestock metabolism studies

Metabolism of indoxacarb using indanone and trifluoromethoxyphenyl ring labelled indoxacarb was investigated in laying hens and lactating cows in the initial DAR.

The characteristics of these studies are summarized in the table below.

Specie	Label position	Number of specimen	Application details		Sampling	
			Duration	Rate	Commodity	Time
Dairy cow	Indanone-1-^{14}C	2	5 days	10 mg/kg diet	Milk (separating into skim milk and cream)	Daily (morning and afternoon)
	trifluoromethoxyphenyl ring -^{14}C	2			Urines and faeces	Daily
					Tissues	6 days

Laying hen	Indanone-1-^{14}C	5	5 days	10 mg/kg diet	Egg (yolk, white)	Daily
	trifluoromethoxyphenyl ring -^{14}C	5			Excreta	Daily
					Tissues	6 days

The metabolism of DPX-JW062 was studied in lactating cows and laying hens. It is noted that the studies were performed with the formulation DPX-JW062 (a racemic mixture of 50% of the insecticidally active enantiomer DPX-KN128 and 50% of the inactive enantiomer IN-KN127), whereas the renewal is intended for DPX-KN128 only.

In both species DPX-JW062 is metabolised extensively. The general metabolic pathways are similar in both species, and involve hydrolysis of the carbomethoxy group, oxidation of the indanone ring, cleavage of the oxidiazine ring, and conjugation. Some minor differences are noted in the metabolic patterns of ruminants and poultry. The general metabolic pathways appeared comparable in the rat and livestock. A certain degree of enrichment of the insecticidally active enantiomer is observed in both species.

In the framework of the peer review, the proposed residue definition was considered to be fat soluble based on the fact that the log Po/w of indoxacarb is higher than 3 (The Netherlands, 2005).

Further information on the nature and occurrence of the metabolite F that was encountered in poultry are still required. In the absence of such information, the residue definition for risk assessment in poultry should be considered as tentative.

2.7.3. Definition of the residue

Residue definition in plant

The residue definition for enforcement and risk assessment in all plant commodities is proposed as the sum of indoxacarb and its *R* enantiomer.

Residue definition in livestock

The submitted information on the metabolism in livestock is considered sufficient to propose a residue definition for animal products:

- the sum of indoxacarb and its R enantiomer for enforcement in all commodities of animal origin;
- the sum of indoxacarb and its R enantiomer for risk assessment in ruminants and pigs;
- the sum of indoxacarb, its R enantiomer and separately its N-decarboxylated metabolite (IN-JT333) for risk assessment in poultry

As the toxicological data available on the metabolite IN-JT333 indicates that the parent toxicity does not cover its toxicity, as a worst-case approach, it is proposed to use the TTC approach. The TTC value for non-genotoxic Cramer class III substances can be used: 0.0015 mg/kg bw/d.

2.7.4. Summary of residue trials in plants and identification of critical GAP

2.7.4.1. Maize

Identification of critical GAP

Crop	Region	Outdoor/ Protected	Application	Number of applications (days interval)	Rate (g as/ha)	BBCH at last application/ PHI
Maize	EU (North and South)	Outdoor	Hydraulic ground directed boom	2 (20days)	37.5	BBCH 34-77

Residue trials

A total 17 residue trials on maize grain are available, 8 were conducted in northern zone of EU and 9 in southern zone of EU; they were conducted in accordance with the intended GAP. All residue levels were below the LOQ of 0.01 mg/kg. 14 residue trials are available on maize forage, 4 were conducted in northern zone of EU and 10 in southern zone of EU according to the intended GAP. Residue levels ranged from 0.14 mg/kg to 0.26 mg/kg in the northern zone and from 0.048 mg/kg to 0.77 mg/kg in the southern zone.

Table 2.7.4-1: Summary of residue data from the supervised residue trials

Summary of monograph and new data supporting the intended use on maize and conformity to existing MRL
Table IIIA 0-1: Summary of monograph and new data supporting the intended use on maize and conformity to existing MRL

Commodity[a]	Region	Outdoor/ Indoor	Individual trial results (mg/kg)		Median residue (mg/kg)	Highest residue (mg/kg)	MRL proposal [b] (mg/kg)	Median CF	Comments
			Enforcement (sum of indoxacarb and its R enantiomer)	Risk assessment (sum of indoxacarb and its R enantiomer)					
Maize grain	NEU	Outdoor	8 × <0.01	8 × <0.01	0.01	0.01	0.01*	1.00	Trials compliant with GAP (DuPont-6006 et 9777).
	SEU	Outdoor	9 × <0.01	9 × <0.01	0.01	0.01	0.01*	1.00	Trials compliant with GAP (DuPont-6006 et 9777).
Maize forage/silage[c]	NEU	Outdoor (4) (14 day PHI)	0.14, 0.18, 0.22, 0.26	0.14, 0.18, 0.22, 0.26	0.200	0.260	0.6	1.00	Trials on maize (sampling at forage stage) compliant with GAP (DuPont-6006/9777&35172)
	SEU	Outdoor (12) (14 day PHI)	0.048, 0.094, 0.11, 0.11, 0.14, 0.18, 0.26, 0.28, 0.32, 0.34, 0.44, 0.77	0.048, 0.094, 0.11, 0.11, 0.14, 0.18, 0.26, 0.28, 0.32, 0.34, 0.44, 0.77	0.220	0.770	1.5	1.00	Rber = 1.860 Rmax = 2.227

SEU outdoor critical GAP: 37.5 g a.s./ha,2 application at latest BBCH 77 with no specified PHI using a DPX-MP062 30WG formulation.

[b] OECD MRL calculator

[c] The OECD Overview document (2009) gives the following definition: Corn forage (field and pop). Cut sample (whole aerial portion of the plant) at late dough/early dent stage (black ring/layer stage for corn only).Growth stages of mono-and dicotyledonous plants from the BBCH monograph, Federal Biological Research Centre for Agriculture and Forestry, 2001 gives the following growth stage descriptions for maize:BBCH 85 Dough stage: kernels yellowish to yellow (variety dependent),about 55% dry matter, BBCH 87 Physiological maturity: black dot/layer visible at base of kernels, about 60% dry matter. Allowing 2 weeks (14 days) for the maize to develop from BBCH 69 (last treatment) to BBCH 86 (mid to late dough stage when maize is typically used as forage) the 14 day forage data is compiled from DuPont-35172 for the evaluations in this table as the data best representative of field corn forage as described by the OECD overview document.

2.7.4.1. Sweet corn

Identification of critical GAP

Crop	Region	Outdoor/ Protected	Application	Number of applications (days interval)	Rate (g as/ha)	BBCH at last application/ PHI
Maize, sweet corn	EU (North and South)	Outdoor	Hydraulic ground directed boom	2 (20days)	37.5	BBCH 34-77

Residue trials

2 residue trials conducted on sweet corn in the southern zone of EU according to the intended GAP are available.

Indoxacarb 150 g/L EC uses on sweet corn are also supported by residue data from the field corn (maize) trials. The EU document "Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs", SANCO 7525/VI/95 - rev.9, March 2011, allows for extrapolation of immature maize data to sweet corn. The milk stage for maize is BBCH 73–79 (Growth stages of mono-and dicotyledonous plants, BBCH monograph, Federal Biological Research Centre for Agriculture and Forestry, 2001). Then, 4 additionally residue trials conducted in southern EU according to the intended GAP are also available. Residue values were selected at BBCH 77 (corresponding to milk stage). One northern residue trials on immature field corn is also available.

All residue levels were below the LOQ of 0.01 mg/kg.

The number of trials conducted in the Northern zone is not sufficient to support the use. A MRL can be proposed based on the SEU trials only.

Table 0-1: Summary of residue data from the supervised residue trials

Commodity	Source	EU zone	Evaluation GAP Residue levels (mg/kg)	STMR (mg/kg)	HR (mg/kg)	Rber (mg/kg)	Rmax (mg/kg)	OECD calculator MRL (mg/kg)
Sweet corn - grain	Overall supporting data	North (1)	Extrapolation from maize grain (immature) **Trials GAP: 2 x 37.5 kg as/ha, BBCH 77** <0.01	0.01	0.01	-	-	0.01*
		South (2)	**Trials GAP: 3 x 37.5 kg as/ha, BBCH 75** <0.01, <0.01	0.01	0.01	-	-	0.01*
		South (4)	Extrapolation from maize grain (immature) **Trials GAP: 2 x 37.5 kg as/ha, BBCH 77** 4x<0.01	0.01	0.01	-	-	0.01*

2.7.4.2. Lettuce

Identification of critical GAP

Crop	Region	Outdoor/ Protected	Application	Number of applications	Rate (g as/ha)	BBCH at last application/

				(days interval)		PHI
Lettuce	EU	outdoor	Hydraulic ground directed boom	4 (7d)	37.5	BBCH 13-49 Seed crops BBCH 13-59 PHI:1 day

Residue trials

A total 15 residue trials on lettuce are available, 8 were conducted in northern zone of EU and 7 in southern zone of EU; they were conducted in accordance with the intended GAP and performed with the active ingredient DPW-KN128 only. Residue levels ranged from 0.14 to 0.85 mg/kg in northern EU and from 0.06 to 0.80 mg/kg in southern EU.

Table 0-2: Summary of residue data from the supervised residue trials

Commodity	Source	EU zone	Evaluation GAP Residue levels (mg/kg)	STMR (mg/kg)	HR (mg/kg)	Rber (mg/kg)	Rmax (mg/kg)	OECD calculator MRL (mg/kg)
Lettuce	Overall supporting data	North (8)	**Trials GAP: 4 x 37.5 kg as/ha, BBCH 16-49, PHI 1d** 0.14, 0.18, 0.27, 0.28, 0.29, 0.45, 0.59, 0.85	0.285	0.850	1.110	1.141	1.5 (1.335)
		South (7) Open leaf variety	**Trials GAP: 4 x 37.5 kg as/ha, BBCH 49, PHI 1d** 0.06, 0.29, 0.35, 0.36, 0.53, 0.67, 0.80	0.360	0.8	1.340	1.284	1.5 (1.433)

It should be noted that according to the results of the bridging trials (study 2-DuPont-33518), residue levels with the racemic mixture would be higher than using only the active ingredient. Therefore, if a MRL is derived only from trials conducted using the technical material according to the new specifications, a MRL exceedance is likely to occur with the current authorizations.

2.7.5. Summary of feeding studies in poultry, ruminants, pigs and fish

The crops intended for the renewal assessment of indoxacarb might be fed to livestock. The median and maximum dietary burdens were therefore calculated for different groups of livestock using the OECD Guidance documents n° 64/32 and 73. The input values for all relevant commodities are summarised in table 2.7.5-1 below.

For maize by-products, default processing factors were not used: as a no-residue situation is expected in maize grain, residues are not expected to concentrate in these processed fractions.

Table 2.7.5-1 : Input values for the dietary burden calculation

Commodity	Median dietary burden		Maximum dietary burden	
	Input value (mg/kg)	Comment	Input value (mg/kg)	Comment
Risk assessment residue definition: the sum of indoxacarb and its *R* enantiomer				
Maize grain	0.01	Median residue	0.01	Median residue
Maize by-products: milled by-products, hominy meal, gluten feed, gluten (meal)	0.01	Median residue	0.01	Median residue
Maize silage/forage	0.22	Median residue	**0.77**	Highest residue

The results of the calculation are reported in the table below.

Table 2.7.5-2 : Results of the dietary burden calculation

	Max dietary burden (mg/kg bw/d)	**Highest contributing commodity**	**Max dietary burden (mg/kg DM)**	**Trigger exceeded?**
Beef cattle	**0.037**	corn field forage/silage	**1.55**	**Yes**
Dairy catte	**0.045**	corn field forage/silage	**1.16**	**Yes**
Sheep (ram/ewe)	0	Corn, field, gluten feed	0.01	No
Sheep (Lamb)	0	Corn, field, gluten feed	0.01	No
Breeding swine	**0.009**	corn field forage/silage	**0.39**	**Yes**
Finishing swine	0	corn field, milled by-products	0.01	No
Poultry-broiler	0.001	corn field, milled by-products	0.01	No
Poultry-layer	**0.014**	corn field forage/silage	**0.20**	**Yes**
Poultry turkey	0.001	corn field, milled by-products	0.01	No

Results show a significant intake for ruminants, pigs and poultries (exceeding the trigger value of 0.004 mg/kg bw/d). The available ruminant feeding study was therefore presented and was used to calculate the expected STMR, HR and MRL values in ruminant matrices.
Regarding swine matrices, as the metabolic fate of indoxacarb residues in rodents and ruminants is considered to be similar, the metabolism findings in ruminants can be extrapolated to pigs.
The following results were obtained, according to the OECD Guidance documents n° 64/32 and 73:

Table 2.7.5-3 : Residue of indoxacarb in ruminant and swine matrix

Animal	**Residues at closet feeding level** (mg/kg)		**Estimated value at 1N level**		**MRL proposal** (mg/kg)
	Mean	Highest	STMR[(b)] (mg/kg)	HR (mg/kg)	
Bovine	Closest feeding level[(a)]:		0,3	mg/kg bw	
	6,7	N Dairy c.	8,1	N Beef c.	
Meat	-	-	0,002	0,033	-
Muscle	0,010	0,010	0,000	0,032	**0,04**
Fat	0,220	0,240	0,010	0,036	**0,04**
Liver	0,010	0,010	0,000	0,001	**0,01***
Kidney	0,010	0,010	0,000	0,001	**0,01***
Milk[(c)]	0,017	0,017	0,001	0,003	**0,01***
Fat per					
Fat Sub.					
Sheep	Closest feeding level[(a)]:		0,3	mg/kg bw	
	647,1	N Lamb	825,0	N Ram/Ewe	
Meat	-	-	0,000	0,000	-
Muscle	0,010	0,010	0,000	0,000	**0,01***
Fat	0,220	0,240	0,000	0,000	**0,01***
Liver	0,010	0,010	0,000	0,000	**0,01***
Kidney	0,010	0,010	0,000	0,000	**0,01***
Milk[(c)]	0,017	0,017	0,000	0,000	**0,01***
Fat per					
Fat Sub.					

Swine	Closest feeding level[(a)]:		0,3	mg/kg bw	
	33,0	N Breeding	857,3	N Finishing	
Meat	-	-	0,000	0,002	-
Muscle	0,010	0,010	0,000	0,000	**0,01***
Fat	0,220	0,240	0,002	0,007	**0,01***
Liver	0,010	0,010	0,000	0,000	**0,01***
Kidney	0,010	0,010	0,000	0,000	**0,01***
Fat per					
Fat Sub.					

Calculated MRL for bovine, sheep and swine are lower than the in force MRLs. Therefore, no new MRLs are proposed in the framework of the renewal.

Table 2.7.5-4 : **Residue of indoxacarb in poultry matrix**

RD monitoring	*sum of indoxacarb and its R enantiomer*				
RD risk assessment	*sum of indoxacarb, its R enantiomer*				
Poultry					
Closest level 0,111 mg/kg bw 8,0 N Layer 134,4 N Turkey	Residues at the closest feeding level (mg/kg)		Estimated value at 1N level		MRL proposal (mg/kg)
	Mean	Highest	STMR (mg/kg)	HR (mg/kg)	
Meat	-	-	0,031	0,033	-
Muscle	0,003	0,003	0,003	0,0038	0,01*
Fat	0,008	0,008	0,000	0,001	0,01*
Liver	0,003	0,003	0,000	0,0003	0,01*
Kidney	0	0,000			
Eggs	0,015	0,015	0,001	0,002	0,01*

RD monitoring	*sum of indoxacarb and its R enantiomer*				
RD risk assessment	*IN-JT333*				
Animal	**Residues at closet feeding level** (mg/kg)		**Estimated value at 1N level**		**MRL proposal** (mg/kg)
	Mean	Highest	STMR[(b)] (mg/kg)	HR (mg/kg)	
Poultry	Closest feeding level(a):		0,111	mg/kg bw	
	7,99450658	N Layer	134	N Turkey	
Meat	-	-	0,003	0,001	-
Muscle	0,003	0,003	0,003	0,000	0,01*
Fat	0,044	0,044	0,002	0,006	0,01*
Liver	0,003	0,003	0,000	0,000	0,01*
Kidney					
Eggs(c)	0,0089	0,0089	0,000	0,001	0,01*

It should be highlighted that the intake calculation for poultry might be underestimated because metabolite F is not considered in the calculation. Considering however that the contribution of poultry products to the exposure is minor, it is rather unlikely that metabolite F would be of concern for consumers.

2.7.6. Summary of effects of processing

As no residues were found in maize and sweet corn grain/kernel at the intended maximum application rate, no studies on the effects of processing on the nature of the residue were considered necessary. Also lettuce is not a crop that undergoes processing.

2.7.7. Summary of residues in rotational crops

Pots containing sandy loam soil were treated with a single application of either one of the radiolabelled forms of DPX-JW062 at a rate of 0.60 kg DPX-JW062/ha (equal to 0.30 kg DPX-KN128/ha). The maximum Predicted Environmental Concentrations (PEC) of indoxacarb in soil (in mg/kg soil) following 4 applications at 37.5 g as/ha on lettuce after 4 years is 0.169 mg/kg. The average concentrations of total residues in the soil were 0.56, 0.25-0.34, 0.25-0.33, and 0.24-0.46 mg eq/kg, after rotational intervals of 0, 36, 90, and 125 days, respectively.
At 36, 90, and 125 days after soil treatment with ^{14}C-labeled DPX-JW062, no single main metabolite component was observed exceeding 0.050 mg/kg. Instead, multiple components, including glucose- and matrix-bound residues, were found in small quantities. Parent compound and the insecticidally active metabolite IN-JT333 were not detected in the crop samples.
However, due to low extraction efficiency in some samples, the RMS believes that further investigations are required on the nature of the bound residues.

2.7.8. Summary of other studies

The data requirement objective of these studies is to determine the residue in pollen and bee products for human consumption resulting from residues taken up by honeybees from crops at blossom.
As no final guidance document related to setting MRLs in honey is available, the effect of indoxacarb on bee products was not tested by the notifier.
However, among crops under consideration, lettuce is not attractive for the bees. Besides, residue trials showed a no residues situation in cereals grain (see section B.7.3). Therefore, no significant residue levels are expected in the blossoms and in the pollen. As maize does not produce nectar, bees are only exposed to pollen residues. Thus, exposure of indoxacarb residues to foraging bees and, consequently, possible residues of indoxacarb in honey or other bee products are considered unlikely to occur.

2.7.9. Estimation of the potential and actual exposure through diet and other sources

When indoxacarb was first peer-reviewed (Review Report SANCO/1408/2001- rev3, 23 september 2005), the acute reference dose (ARfD) was set at 0.125 mg/kg bw/d in view of the hazard profile of the substance. Nevertheless, it is now considered appropriate to set an ARfD at 0.005 mg/kg bw/d (Volume 1, part 2.6.12).

Table 2.7.9-1 : Toxicological reference values relevant for dietary risk assessment

End-Point	Value	Study	Safety Factor	Reference
sum of indoxacarb and its *R* enantiomer				
Acceptable Daily Intake (ADI)	0.005 mg/kg bw/d	Rat, developmental study with DPX-KN128 (99:1), supported by short-term toxicity studies in rats and dogs	100	

End-Point	Value	Study	Safety Factor	Reference
sum of indoxacarb and its *R* enantiomer				
Acute Reference Dose (ARfD)	0.005 mg/kg bw/d	Rat, developmental study with DPX-KN128 (99:1)	100	
IN-JT333 (provisional TTC approach pending a 28-day repeated-dose toxicity study with IN-JT333 (OECD 407))				
Acceptable Daily Intake (ADI) and accute reference dose (ARfD)	0.0015 mg/kgbw/d	TTC value for non-genotoxic Cramer class III substances		

The consumer risk assessment was performed using revision 2 of the EFSA PRIMo (Pesticide Residue Intake Model). For the chronic and acute intake assessment the proposed MRL, STMR and HR derived from residue trials were considered for plant and animal commodities
For poultry, considering the metabolite IN-JT333 as included in the residue definition for risk assessment, a conversion factor can be derived.

Table 2.7.9-2 : Input values for the consumer risk assessment

Commodity	Chronic risk assessment		Acute risk assessment	
	Input value (mg/kg)	Comment	Input value (mg/kg)	Comment
sum of indoxacarb and its *R* enantiomer				
Maize grain	0.01	Calculated MRL	0.01	Calculated HR
Sweet corn	0.01	Calculated MRL	0.01	Calculated HR
lettuce	1.5	Calculated MRL	0.85	Calculated HR
sum of indoxacarb and its R enantiomer				
Bovine meat	**0.056**	Calculated MRL	**0.056**	Calculated HR
Bovine fat	**0.05**	Calculated MRL	**0.048**	Calculated HR
Bovine liver	**0.01**	Calculated MRL	**0.01**	Calculated HR
Bovine kidney	**0.01***	Calculated MRL	**0.01***	Calculated HR
milk	**0.01***	Calculated MRL	**0.01**	Calculated HR
Sheep meat	**0.056**	Calculated MRL	**0.056**	Calculated HR
Sheep muscle	**0.01***	Calculated MRL	**0.01***	Calculated HR
Sheep fat	**0.02**	Calculated MRL	**0.02**	Calculated HR
Sheep liver	**0.01**	Calculated MRL	**0.01**	Calculated HR
Sheep kidney	**0.01***	Calculated MRL	**0.01***	Calculated HR
Swine meat	**0.06**	Calculated MRL	**0.056**	Calculated HR
Swine muscle	**0.01***	Calculated MRL	**0.01***	Calculated HR
Swine fat	**0.03**	Calculated MRL	**0.026**	Calculated HR
Swine liver	**0.01**	Calculated MRL	**0.01**	Calculated HR
kidney	**0.01***	Calculated MRL	**0.01***	Calculated HR
Poultry meat	**0.01***	Calculated MRL	**0.01***	Calculated HR
Poultry muscle	**0.01***	Calculated MRL	**0.01***	Calculated HR
Poultry fat	**0.01***	Calculated MRL	**0.01***	Calculated HR

Commodity	Chronic risk assessment		Acute risk assessment	
	Input value (mg/kg)	Comment	Input value (mg/kg)	Comment
Poultry liver	**0.01***	Calculated MRL	**0.01***	Calculated HR
Eggs	**0.01***	Calculated MRL	**0.01***	Calculated HR
Second Risk assessment residue definition: IN-JT333 (Poultry only).				
Poultry meat	**0.01***	Calculated MRL	**0.01***	Calculated HR
Poultry muscle	**0.01***	Calculated MRL	**0.01***	Calculated HR
Poultry fat	**0.01***	Calculated MRL	**0.01***	Calculated HR
Poultry liver	**0.01***	Calculated MRL	**0.01***	Calculated HR
Eggs	**0.01***	Calculated MRL	**0.01***	Calculated HR

(1) As the log POW for indoxacarb (DPX-KN128) is 4.65, MRL on poultry meat was calculated as follow: MRL meat = 10% fat + 90% muscle.

Considering residue definition for risk assessment, the diet with the highest TMDI is “ES adult” with 19.2 % of the ADI. Therefore no chronic health effects are expected. An acute risk was identified on lettuce with an IESTI of 457.4 % of the ARfD.

RMS proposes to use the TTC approach in order to realize a provisionally estimation of the dietary risk assessment. However, the proposed TTC values are only tentative and additional work is still required to define this value with better confidence.

Table 2.7.9-3 : TMDI calculation linked to representative uses

Sum of indoxacarb and its R enantiomer

Chronic risk assessment - refined calculations								
			TMDI (range) in % of ADI minimum - maximum					
			0		18			
			No of diets exceeding ADI:	---				
Highest calculated TMDI values in % of ADI	MS Diet		Highest contributor to MS diet (in % of ADI)	Commodity / group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity / group of commodities	3rd contributor to MS diet (in % of ADI)	Commodity / group of commodities
17,6	ES adult		16,1	Lettuce	1,0	Milk and milk products: Cattle	0,1	Bovine: Meat
16,1	ES child		12,5	Lettuce	2,5	Milk and milk products: Cattle	0,3	Bovine: Meat
13,2	WHO regional European diet		11,3	Lettuce	1,0	Milk and milk products: Cattle	0,3	Swine: Meat
12,6	WHO Cluster diet B		10,8	Lettuce	0,6	Milk and milk products: Cattle	0,5	Maize
11,3	IT adult		11,3	Lettuce	0,0	Maize	0,0	Sweet corn
10,5	WHO Cluster diet F		9,0	Lettuce	0,8	Milk and milk products: Cattle	0,2	Swine: Meat
9,7	NL child		5,9	Milk and milk products: Cattle	2,9	Lettuce	0,3	Swine: Meat
8,7	IT kids/toddler		8,7	Lettuce	0,0	Maize	0,0	Sweet corn
5,5	FR infant		5,1	Milk and milk products: Cattle	0,1	Bovine: Meat	0,1	Poultry: Meat
5,4	NL general		3,6	Lettuce	1,3	Milk and milk products: Cattle	0,2	Swine: Meat
5,3	DE child		2,9	Milk and milk products: Cattle	1,9	Lettuce	0,2	Eggs: Chicken
4,3	DK child		4,2	Lettuce	0,0	Bovine: Liver	0,0	Sweet corn
4,2	UK vegetarian		4,2	Lettuce	0,0	Sweet corn	0,0	Poultry: Meat
4,1	WHO cluster diet E		2,8	Lettuce	0,6	Milk and milk products: Cattle	0,2	Poultry: Meat
4,0	IE adult		2,6	Lettuce	0,6	Milk and milk products: Cattle	0,5	Maize
3,6	FR all population		2,8	Lettuce	0,5	Milk and milk products: Cattle	0,1	Poultry: Meat
3,5	UK Adult		3,5	Lettuce	0,0	Sweet corn	0,0	Bovine: Liver
3,1	LT adult		1,9	Lettuce	0,8	Milk and milk products: Cattle	0,2	Swine: Meat
2,7	SE general population 90th percentile		2,5	Milk and milk products: Cattle	0,2	Eggs: Chicken	0,0	Sweet corn
2,3	FI adult		2,3	Lettuce	0,0	Maize		FRUIT (FRESH OR FROZEN)
1,5	WHO cluster diet D		0,9	Milk and milk products: Cattle	0,1	Bovine: Meat	0,1	Maize
0,7	FR toddler		0,3	Bovine: Meat	0,2	Eggs: Chicken	0,2	Poultry: Meat
0,6	UK Toddler		0,6	Lettuce	0,0	Sweet corn	0,0	Bovine: Liver
0,4	PL general population		0,4	Lettuce	0,0	Maize		FRUIT (FRESH OR FROZEN)
0,2	UK Infant		0,2	Maize	0,0	Bovine: Liver	0,0	Sweet corn
0,1	DK adult		0,1	Bovine: Meat	0,0	Bovine: Liver	0,0	Sweet corn
0,1	PT General population		0,1	Maize		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)

N-decarboxylated metabolite (IN-JT333)

Chronic risk assessment								
		TMDI (range) in % of ADI minimum - maximum		1				
		No of diets exceeding ADI:	---					
Highest calculated TMDI values in % of ADI	MS Diet	Highest contributor to MS diet (in % of ADI)	Commodity / group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity / group of commodities	3rd contributor to MS diet (in % of ADI)	Commodity / group of commodities
1,3	ES child	0,9	Poultry: Meat	0,5	Eggs: Chicken		FRUIT (FRESH OR FROZEN)
1,3	WHO regional European diet	0,6	Poultry: Meat	0,4	Eggs: Chicken	0,3	Poultry: Fat
1,2	FR toddler	0,7	Eggs: Chicken	0,6	Poultry: Meat		FRUIT (FRESH OR FROZEN)
1,1	DE child	0,7	Eggs: Chicken	0,4	Poultry: Meat		FRUIT (FRESH OR FROZEN)
1,1	WHO cluster diet E	0,7	Poultry: Meat	0,4	Eggs: Chicken	0,0	Poultry: Fat
1,0	WHO Cluster diet B	0,7	Poultry: Meat	0,3	Eggs: Chicken	0,0	Poultry: Fat
0,9	NL child	0,5	Poultry: Meat	0,4	Eggs: Chicken	0,0	Poultry: Liver
0,7	ES adult	0,4	Poultry: Meat	0,3	Eggs: Chicken		FRUIT (FRESH OR FROZEN)
0,7	FR infant	0,4	Poultry: Meat	0,3	Eggs: Chicken		FRUIT (FRESH OR FROZEN)
0,6	WHO Cluster diet F	0,3	Eggs: Chicken	0,3	Poultry: Meat	0,0	Poultry: Fat
0,6	FR all population	0,4	Poultry: Meat	0,2	Eggs: Chicken		FRUIT (FRESH OR FROZEN)
0,6	SE general population 90th percentile	0,6	Eggs: Chicken		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)
0,5	WHO cluster diet D	0,3	Eggs: Chicken	0,3	Poultry: Meat		FRUIT (FRESH OR FROZEN)
0,4	LT adult	0,2	Eggs: Chicken	0,2	Poultry: Meat		FRUIT (FRESH OR FROZEN)
0,4	IE adult	0,2	Poultry: Meat	0,2	Eggs: Chicken		FRUIT (FRESH OR FROZEN)
0,4	NL general	0,2	Poultry: Meat	0,2	Eggs: Chicken	0,0	Poultry: Liver
0,0	UK vegetarian	0,0	Poultry: Meat		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)

Table 2.7.9-4 : IESTI calculation linked to representative uses only.
Sum of indoxacarb and its R enantiomer

Acute risk assessment /children - refined calculations						Acute risk assessment / adults / general population - refined calculations					
The acute risk assessment is based on the ARfD.											
For each commodity the calculation is based on the highest reported MS consumption per kg bw and the corresponding unit weight from the MS with the critical consumption. If no data on the unit weight was available from that MS an average European unit weight was used for the IESTI calculation.											
In the **IESTI 1** calculation, the variability factors were 10, 7 or 5 (according to JMPR manual 2002), for lettuce a variability factor of 5 was used. In the **IESTI 2** calculations, the variability factors of 10 and 7 were replaced by 5. For lettuce the calculation was performed with a variabilty factor of 3.											
Threshold MRL is the calculated residue level which would leads to an exposure equivalent to 100 % of the ARfD.											
No of commodities for which ARfD/ADI is exceeded (IESTI 1)		**1**	**No of commodities for which ARfD/ADI is exceeded (IESTI 2)**		**1**	**No of commodities for which ARfD/ADI is exceeded (IESTI 1)**		**1**	**No of commodities for which ARfD/ADI is exceeded (IESTI 2)**		**1**
IESTI 1	***)**	****)**	**IESTI 2**	***)**	****)**	**ESTI 1**	**)**	****)**	**IESTI 2**	***)**	****)**
Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)
457,4	Lettuce	0,85 / 0,18	274,4	Lettuce	0,85 / 0,3	186,8	Lettuce	0,85 / 0,45	112,1	Lettuce	0,85 / 0,75
24,8	Milk and milk	0,01 / -	24,8	Milk and milk	0,01 / -	15,0	Poultry: Meat	0,064 / -	15,0	Poultry: Meat	0,064 / -
14,7	Sweet corn	0,01 / -	14,4	Poultry: Meat	0,064 / -	5,6	Swine: Meat	0,056 / -	5,6	Swine: Meat	0,056 / -
14,4	Poultry: Meat	0,064 / -	10,5	Sweet corn	0,01 / -	4,8	Bovine: Meat	0,04 / -	4,8	Bovine: Meat	0,04 / -
10,2	Bovine: Meat	0,04 / -	10,2	Bovine: Meat	0,04 / -	4,4	Sweet corn	0,01 / -	3,4	Milk and milk products: Cattle	0,01 / -
No of critical MRLs (IESTI 1)		1				**No of critical MRLs (IESTI 2)**		1			
No of commodities for which ARfD/ADI is exceeded		**---**				**No of commodities for which ARfD/ADI is exceeded**		**---**			
		*****)**						*****)**			
Highest % of ARfD/ADI	Processed commodities	pTMRL/ threshold MRL (mg/kg)				Highest % of ARfD/ADI	Processed commodities	pTMRL/ threshold MRL (mg/kg)			
0,9	Maize flour	0,01 / -				0,1	Maize flour	0,01 / -			

N-decarboxylated metabolite (IN-JT333)

Acute risk assessment /children						Acute risk assessment / adults / general population					
The acute risk assessment is based on the ARfD.											
For each commodity the calculation is based on the highest reported MS consumption per kg bw and the corresponding unit weight from the MS with the critical consumption. If no data on the unit weight was available from that MS an average European unit weight was used for the IESTI calculation.											
In the **IESTI 1** calculation, the variability factors were 10, 7 or 5 (according to JMPR manual 2002), for lettuce a variability factor of 5 was used. In the **IESTI 2** calculations, the variability factors of 10 and 7 were replaced by 5. For lettuce the calculation was performed with a variabilty factor of 3.											
Threshold MRL is the calculated residue level which would leads to an exposure equivalent to 100 % of the ARfD.											
No of commodities for which ARfD/ADI is exceeded (IESTI 1)		---	**No of commodities for which ARfD/ADI is exceeded (IESTI 2)**		---	**No of commodities for which ARfD/ADI is exceeded (IESTI 1)**		---	**No of commodities for which ARfD/ADI is exceeded (IESTI 2)**		---
IESTI 1	*)	**)	**IESTI 2**	*)	**)	**ESTI 1**	)	**)	**ESTI 2**	)	**)
Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)
7,5	Poultry: Meat	0,01 / -	7,5	Poultry: Meat	0,01 / -	7,8	Poultry: Meat	0,01 / -	7,8	Poultry: Meat	0,01 / -
						3,0	Poultry: Liver	0,01 / -	3,0	Poultry: Liver	0,01 / -

2.7.10. Proposed MRLs and compliance with existing MRLs

Crops	Proposed MRL (mg/kg)	MRL according Reg. EU No 2015/845
Maize	0.01*	0.01*
Sweet corn	0.01*	0.02*

If the new toxicological value proposed is agreed at EU level, this lead to the necessity of reviewing the current MLR. Moreover, the new MRL calculated from considered trials on lettuce also shows an exceedance of the 100% of the new ARfD. FR will therefore recommend a review of the all existing MRL for indoxacarb.

2.7.11. Proposed import tolerances and compliance with existing import tolerances

Not relevant.

2.8. FATE AND BEHAVIOUR IN THE ENVIRONMENT

2.8.1. Summary of fate and behaviour in soil

Under aerobic soil condition, the route of degradation of indoxacarb (DPX-KN128) was studied using radiolabelled [TFMP-^{14}C]/[Ind-^{14}C] DPX-JW062 and DPX-MP062 in a variety of aerobic soils, from four laboratory studies. These four laboratory studies were submitted in the original DAR, and no new studies were submitted for the purpose of renewal. Updated assessment of these studies revealed some uncertainties in the analytical results (unidentified radioactivity, variation of the isomeric ratio). They were however still considered valid but a data gap is proposed by RMS for further investigation on the identification and characterization of unidentified polar fraction and further investigation on identity of metabolite IN-ML437-OH in the study of Singles (2002). It is RMS and co-RMS opinion that this data gap could be addressed with an additional soil metabolism study with active isomer DPX-KN128 on similar soil, with correct mass balance and peaks identification to confirm residue definition for risk assessment.
Some of the data were excluded from the kinetic evaluation for deriving degradation rate.

The proposed degradation pathway of indoxacarb in aerobic soil is shown in Figure 2.8.1-1. Degradation of indoxacarb proceeds by 3 major pathways: demethylation followed by N-decarboxylation to form IN-JT333, ester hydrolysis to form IN-KT413, and opening of the oxadiazine ring to form IN-KG433. These primary metabolites also degrade further. IN-JT333 undergoes additional transformation *via* opening of the oxadiazine ring to form IN-JU873. IN-JU873 proceeds through de-esterification and decarboxylation reactions and a ring closure to form IN-ML438. Both IN-JU873 and IN-ML438 are further transformed by bridge cleavage to form IN-MK643 and IN-MK638. IN-KG433 degraded *via* N-decarboxylation to form IN-JU873, and also cleavage of the urea bridge to form IN-KB687. IN-KT413 rearranged to form IN-MP819, which also rearranged to form IN-ML438. Mineralisation to $^{14}CO_2$ (maximum of 35.7% AR) and formation of non-extractable (bound) residues (maximum of 74.7% AR) were significant degradation processes.

The significance of the various metabolites varies in the different soils and is most likely due to variability in the composition of the microbial populations between soils. Based on the various soil metabolism studies, the overall maximum occurrences of IN-KT413, IN-KG433, IN-JT333, IN-

JU873, IN-KB687, IN-ML438, IN-MK643, IN-MK638, and IN-MP819 were 18.4%, 39.7%, 18.6%, 12.9%, 6.9%, 9.7%, 12.0%, 28.1%, and 1.9% of the applied radioactivity (AR).

The major metabolites of indoxacarb in laboratory soils are IN-KT413, IN-KG433, IN-JT333, IN-JU873, IN-ML438, IN-MK643, and IN-MK638. IN-KB687 is a minor non transient metabolite. These eight metabolites are including in residue definition for risk assessment in soil, ground water and surface water.

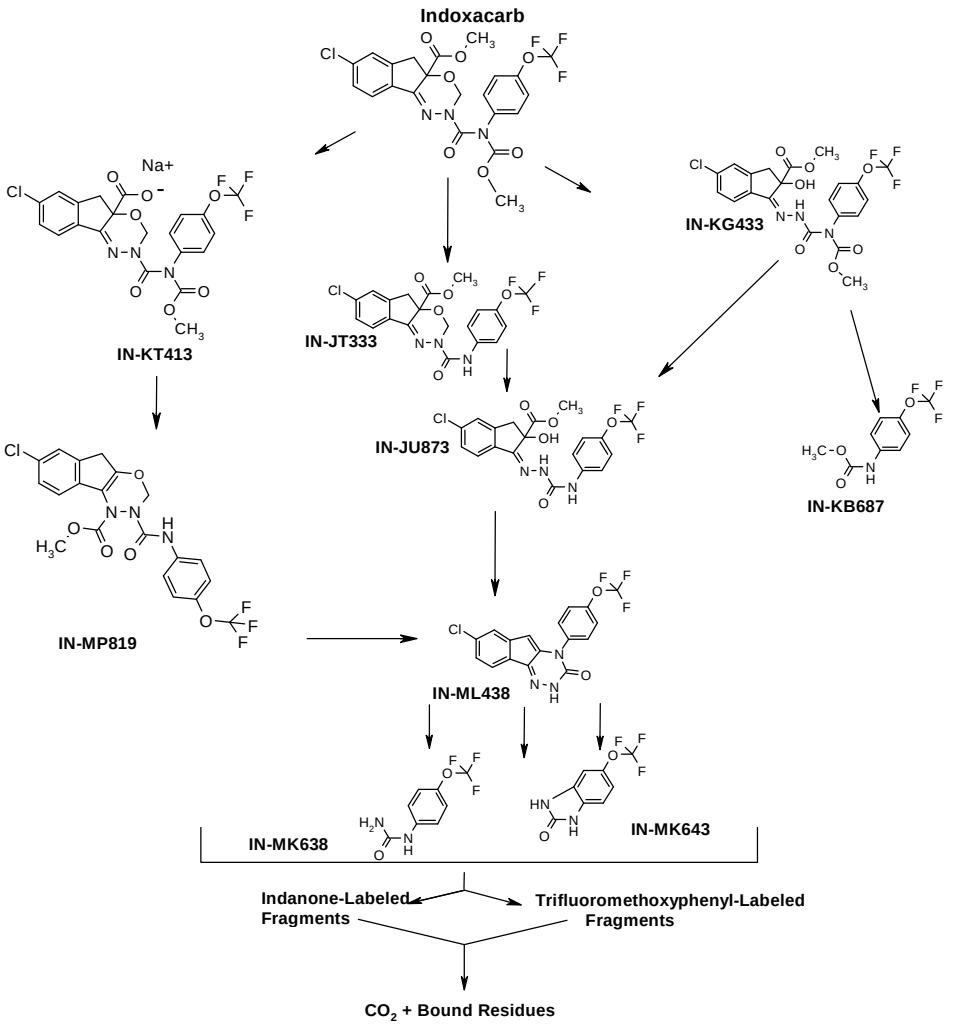


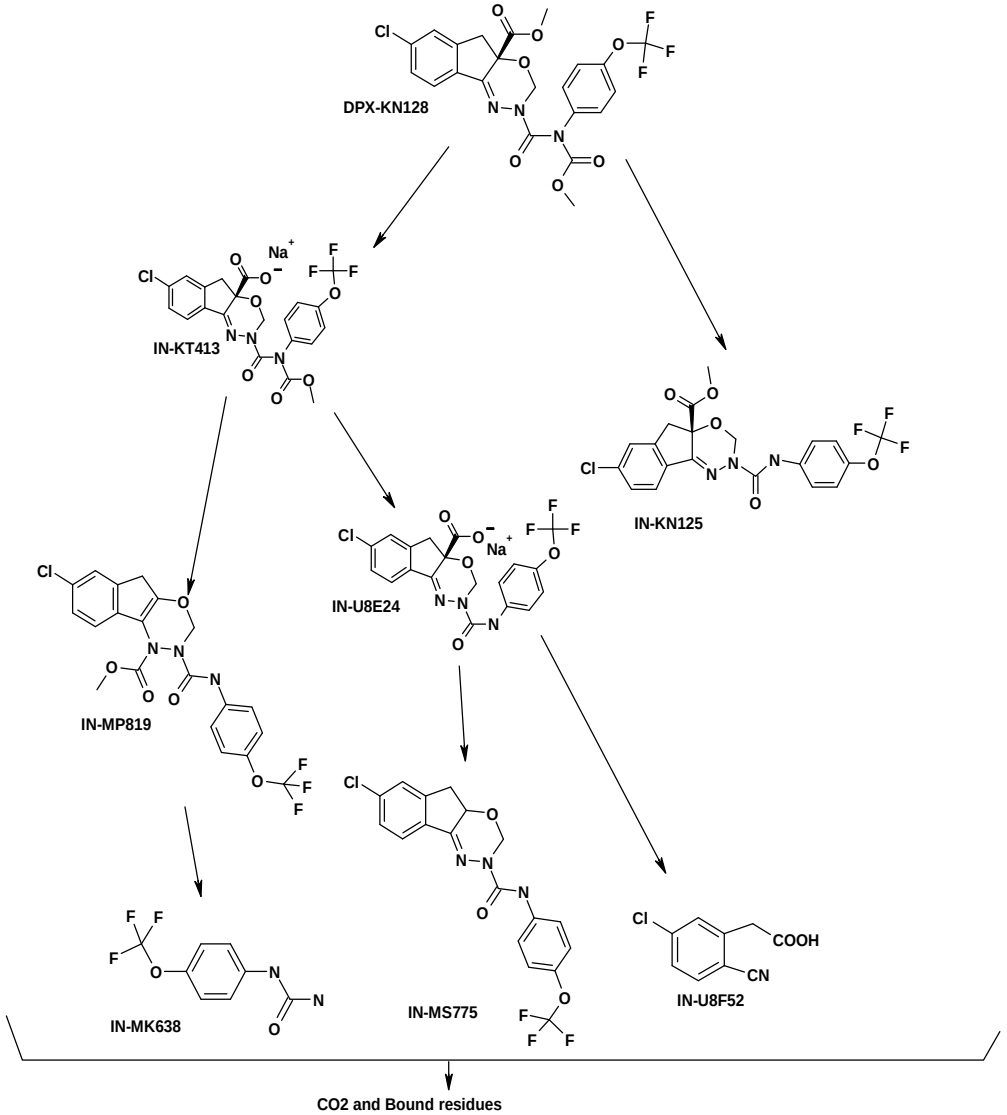
Figure 2.8.1-1 : Proposed degradation pathway of indoxacarb in aerobic soil

Under anaerobic conditions, the route of degradation of indoxacarb was studied using radiolabelled IN-KN128 (S-enantiomer of Indoxacarb).

The major transformation products detected were IN-KT413, IN-U8E24, IN-MP819, IN-KN125, IN-MS775, IN-U8F52, and IN-MK638, with observed maximum concentrations of 25.2, 40.0, 5.9, 10.6, 35.4, 14.7, and 9.4% of the applied radioactivity (AR), respectively. It is noted that metabolite IN-U8E24 reached its maximum concentration during the anaerobic phase of the study (40.0%) but also reached the concentration of 13.8% at DAT 2 during the preliminary aerobic phase of the study. It is thus considered as potential aerobic major metabolite and is included in the residue definition for risk assessment for soil and groundwater.

Proposed degradation pathway of indoxacarb in anaerobic soil is shown in Figure 2.8.1-2 Indoxacarb underwent ester hydrolysis to form IN-KT413 and IN-KN125 (S-enantiomer of IN-JT333; IN-JT333 is a mixture of IN-KN125 and IN-KN124, the break down product of IN-KN127) via demethylation N-decarboxylation. IN-KT413 also underwent decarboxylation and rearrangement of the N-methylester group to form IN-MP819. IN-MP819 further degraded to IN-MK638 through oxadiazine ring opening and bridge cleavage. IN-KT413 could degrade via demethylation N-decarboxylation to form IN-U8E24. Decarboxylation of IN-U8E24 led to the formation of the residue IN-MS775. IN-U8F52 was formed from IN-U8E24 via indanone ring opening. Formation of non-extractable (bound) residues (maximum of 37.3% AR) was also a significant degradation process.

Figure 2.8.1-2 Proposed degradation pathway of indoxacarb in anaerobic soil



Note: IN-KN125 is S-enantiomer of IN-JT333

Soil photolysis of indoxacarb was studied using radiolabelled DPX-JW062. Under photolytic conditions, the main reaction was cleavage of the amide bond to form IN-KB687 (maximum of 22% of applied radioactivity). A minor reaction was the formation of IN-JT333 (maximum of 2.5% of the applied radioactivity) *via* N-decarboxylation. A small amount of CO_2 was also generated (maximum of 4.5% applied radiolabel). Soil photolysis is not expected to be a significant environmental degradation process, since the rate of degradation due to photolysis was essentially the same as the rate measured in the dark control.

Rates of degradation in laboratory

The rates of aerobic degradation of indoxacarb and its metabolites in the laboratory were calculated in a new kinetic evaluation which meets the current guidance of the FOCUS workgroup on degradation kinetics (FOCUS 2006).

Indoxacarb

The rate of aerobic degradation of indoxacarb was calculated in 5 different soils and conditions that were found to be reliable for kinetic purpose. $DegT_{50}$ and $DegT_{90}$ values for indoxacarb using FOMC and DFOP kinetics ranged from 2.4 to 10.3 days at 20°C and from 15.7 to 404.7 days, respectively. Normalised SFO or pseudo-SFO $DegT_{50}$ value ranged from 4.8 to 164.5 days and geomean of 32.4 days was retained for modelling purpose.

Metabolites

For metabolites, laboratory rate of degradation studies with metabolite directly applied were available for the following: IN-KT413, IN-KG433, IN-JT333, IN-JU873, IN-KB687, IN-ML438, IN-MK643 and IN-MK638. In addition, attempts were made to derive DT_{50} data for every metabolite from the laboratory degradation studies performed with indoxacarb as the applied test material, but only some of the fits results for IN-JT333 and IN-ML438 were found reliable.

$DegT_{50}$ and $DegT_{90}$ values for the metabolite IN-JT333 using SFO, FOMC and DFOP kinetics ranged from 4.3 to 34.6 days and from 37.8 to 228.8 days, respectively. Normalised SFO or pseudo-SFO $DegT_{50}$ value ranged from 5.0 to 111 days and geomean of 16.3 days was retained for modelling purpose. The values were derived from metabolite applied studies and indoxacarb laboratory degradation studies.

$DegT_{50}$ and $DegT_{90}$ values for the metabolite IN-KG433 using FOMC and DFOP kinetics ranged from 1.6 to 2.5 days and from 13.1 to 57.8 days, respectively. Normalised SFO or pseudo-SFO $DegT_{50}$ value ranged from 2.6 to 17.4 days and geomean of 4.2 days was retained for modelling purpose. The values were derived from metabolite applied studies only.

$DegT_{50}$ and $DegT_{90}$ values for the metabolite IN-MK638 using SFO and DFOP kinetics ranged from 4.8 to 17.3 days and from 16.1 to 57.5 days, respectively. Normalised SFO or pseudo-SFO $DegT_{50}$ value ranged from 4.0 to 16.0 days and geomean of 8.0 days was retained for modelling purpose. The values were derived from metabolite applied studies only.

$DegT_{50}$ and $DegT_{90}$ values for the metabolite IN-MK643 using SFO kinetics ranged from 123.3 to 314.2 days and from 490.6 to 1043.8 days, respectively. Normalised SFO $DegT_{50}$ value ranged from 88.7 to 314.2 days and geomean of 169.5 days was retained for modelling purpose. The values were derived from metabolite applied studies only.

$DegT_{50}$ and $DegT_{90}$ values for the metabolite IN-ML438 using SFO and DFOP kinetics ranged from 40.6 to 107.1 days and from 241.9 to 507.7 days, respectively. Normalised SFO or pseudo-SFO $DegT_{50}$ value ranged from 80.9 to 172.8 days and geomean of 186.5 days was retained for modelling purpose. The values were derived from metabolite applied studies and indoxacarb laboratory degradation studies.

$DegT_{50}$ and $DegT_{90}$ values for the metabolite IN-JU873 using DFOP kinetics ranged from 10.0 to 32.8 days and from 66.4 to 242.5 days, respectively. Normalised SFO $DegT_{50}$ value ranged from 15.6 to 47.2 days and geomean of 32.1days was retained for modelling purpose. The values were derived from metabolite applied study only.

$DegT_{50}$ and $DegT_{90}$ values for the metabolite IN-KB687 using SFO and FOMC kinetics were 0.67 and 0.56 days and from 2.21 to 1.85 days, respectively (only two reliable values). Normalised SFO $DegT_{50}$ value were 0.51 and 0.67 days and worst-case value of 0.67 days was retained for modelling purpose.

$DegT_{50}$ and $DegT_{90}$ values for the metabolite IN-KT413 using DFOP and FOMC kinetics ranged from 0.6 to 4.0 days and from 2.6 to 20.5 days, respectively. Normalised SFO $DegT_{50}$ value ranged from 0.6 to 3.7 days and geomean of 1.7 days was retained for modelling purpose. The values were derived from metabolite applied study only.

Based on the DT_{50} values (2.4 to 10.3 days) measured under laboratory conditions, there is little chance of accumulation of indoxacarb under realistic environmental conditions. However, based on the DT_{90} and/or $DegT_{50}$ for indoxacarb and some metabolites, field dissipation trials are triggered for the following items:

- Indoxacarb, with maximum persistence DT_{90} of 404.7 d (DFOP)
- IN-JT333, with maximum persistence DT_{90} of 228.8 d (DFOP)
- IN-JU873, with maximum persistence DT_{90} of 156.8d (SFO)
- IN-ML438, with maximum persistence DT_{50} and DT_{90} of 109.5d and 363.7d (SFO)
- IN-MK643, with maximum persistence DT_{50} and DT_{90} of 314.2d and 1043.8d (SFO)

Field dissipation studies

Field soil dissipation studies were conducted at 4 sites in Europe using Indoxacarb (DPX-KN128) 30WG: Bühren, Germany; Graffignana, Italy; Termens, Spain; and Douai, France. The metabolites were chosen based on the major metabolites observed from the laboratory metabolism studies. All metabolites monitored (IN-KT413, IN-JU873, IN-JT333, IN-KG433, IN-KB687, IN-MK463, and IN-MK638) with the exception of IN-JU873 were detected during the course of the study, which confirmed the degradation profile observed from the laboratory studies.

Indoxacarb as well as the metabolites' residues found were generally confined to the upper soil segments (0 15 cm), with the highest concentration found in the 0–5 cm segment at every sampling. This demonstrates a low leaching potential for indoxacarb. These conclusions are consistent with high Koc (Koc = 5125 mL/g).

The DT_{50} values (ranged from 7.08 to 9.4 days) were calculated for the parent compound, indicating a rapid dissipation of indoxacarb under field conditions. These field dissipation rates are also similar to the DT_{50} values (range from 2.4 to 10.3 days) estimated from laboratory study conditions at 20°C.

No normalized DT_{50} were derived from these field data, although the trials were performed according to EFSA (2014) guidance. RMS is of the opinion that normalized DT_{50} should be derived and would allow addressing some of remaining uncertainities concerning the stability of the isomeric ratio, and the robustness of the original laboratory data to derive DT_{50}. Since irrigation was made after 1st sampling at days 0, normalised DT50 should be derived from DAT3.

Mobility

Adsorption of indoxacarb was measured in a batch equilibrium study on 4 soils. Adsoprtion constant was not determined according to Freundlich isotherm since definitive test was performed at a single water concentration. Linear Koc values ranged between 2500 and 9 600 mL/g (arithmetic mean: 5125 mL/g). In the absence of any updated study, and considering that this Kdoc data however reflects strong adosprtion to soil, this value was kept for risk assessment. According to McCall classification, indoxacarb is considered as slightly mobile to immobile in soil. No pH dependence was identified.

The batch equilibrium adsorption studies suggest that the major soil metabolites of indoxacarb are moderately to strongly sorbed to soil. IN-JT333 has an average K_{oc} of 17300 mL/g, IN-KT413 has an average K_{foc} of 344 mL/g, IN-KG433 has an average K_{foc} of 314 mL/g, IN-JU873 has an average K_{foc} of 16883 mL/g, IN-MK643 has an average K_{foc} of 269 mL/g, IN-MK638 has an average K_{foc} of 151 mL/g, IN-ML438 has an average K_{oc} of 18697 mL/g, and IN-KB687 had an average K_{foc} of 237.2 mL/g.

Koc value for metabolite IN-U8E24 was estimated to be 1910 mL/g with EPIsuite, but this value was found to be probably overestimated by RMS, when comparing Koc value obtained with EPIsuite and Kfoc value obtained from batch equilibrium study for metabolite IN-KT413. This Koc value from EPIsuite is thus not considered as reliable for risk assessment. A data gap for reliable Koc from batch equilibrium study is proposed.

2.8.2. Summary of fate and behaviour in water and sediment

Route of degradation in water and sediment

The hydrolysis of indoxacarb (DPX-KN128) in sterile buffer solutions was temperature and pH dependent. Indoxacarb degraded most rapidly at pH 9, followed by pH 7. Indoxacarb was shown to be hydrolytically stable at acidic pH 4. At pH 7, the DT_{50} values of indoxacarb were 68.9, 17.6, and 5.6 days for 10, 20, and 30°C, respectively. At pH 9, the DT_{50} values of indoxacarb were 0.99, 0.37, and 0.14 days for 10, 20, and 30°C, respectively. Hydrolysis products measured at greater than 10% of the applied were IN-KT413 and IN-MP819.

The aqueous photodegradation of indoxacarb was investigated in pH 5 buffer at 25°C under simulated sunlight (xenon arc light). Indoxacarb is rapidly degraded by photolysis in pH 5 sterile buffer (DT_{50} of approximately 3 days under continuous irradiation and 4.5 days when adjusted to sunlight-equivalent days). The major degradation products were IN-C0639 (maximum of 10.2% AR), IN-MA573 (maximum of 19.9% AR), IN-MH304 (maximum of 32.3% AR), IN-KB687 (maximum of 15% AR), IN-MF014 (maximum of 37.6% AR), and numerous minor components.

The aerobic mineralisation of radiolabelled indoxacarb (DPX-KN128) was studied in one natural surface water system from North America under pelagic conditions at 20 ± 2°C in the dark. The main transformation products detected were IN-KT413 (88.6% AR (Day 28)); IN-MP819 (4.9% AR (Day 45)), IN-MK638 (8.5% AR (Day 60)), and IN-P0036 (5.4% AR (Day 60)). Indoxacarb degraded to undetectable level by the end of the incubation period with SFO DT_{50} of 5.93 days

Based on the results of the biodegradability test, indoxacarb is not ready biodegradable.

The proposed major degradation pathway of indoxacarb in four water/sediment system systems (two system from old study and two systems in new study) is demonstrated in Figure 2.8.2-1 where indoxacarb is basically degraded via 3 major pathways. The degradation pathway of indoxacarb in water was the same for all four systems and indoxacarb hydrolysed to form IN-KT413 as the most significant metabolite in water. In sediment (similar to aerobic soil condition), indoxacarb was transformed to IN-JT333/IN-KN125 (S-enantiomer of IN-JT333) via demethylation followed by N-decarboxylation, and to IN-KG433 via oxadiazine ring cleavage of indoxacarb. IN-KT413 underwent decarboxylation and rearrangement of the N-methylester group to form IN-MP819 in sediment. IN-KT413 degraded via demethylation N-decarboxylation to form IN-U8E24. IN-MP819 further degraded to IN-MK638 through oxadiazine ring opening and bridge cleavage. Decarboxylation and cleavage of IN-U8E24 led to the formation of the residue IN-MS775 and IN-UYG24, respectively. IN-JT333 could also be transformed to IN-MS775 via demethylation followed by decarboxylation.

The major degradation pathway between the old and the new study was similar. However, much more hydrolytical metabolite IN-KT413 was detected from the new study, which could be caused by the dose rate. The water/sediment system from previous study was dosed at a nominal rate of 0.5 µg/mL in water (greater than the water solubility of indoxacarb, 0.2 µg/mL) and the dose rate for new study was 0.2 µg/mL in water (equal to the water solubility). When dosed at rates above solubility, the test material dissipated rapidly from the water phase of both systems (DT_{50} in water phase ranged from 0.5 to 0.6 days) with 55.1 to 62.5% AR indoxacarb extracted from sediment phase at Day 0, resulting in more metabolites formed in sediment including IN-JT333, IN-KG433, and IN-MS775. While dosed at the solubility of 0.2 µg/mL, a relatively slow transfer rate (DT_{50} in water phase ranged from 0.8 to 1.0 days) was observed from both systems with nearly 90% AR indoxacarb remained in water phase, resulting in significant hydrolytical metabolite IN-KT413 formed (maximum of 83.0% AR, with maximum of 74.7% AR in water), and then further degraded to IN-MP819, IN-U8E24, and transient water soluble metabolite IN-UYG24.

While the rate of photolytic degradation of indoxacarb was rapid in sterile buffers (DT_{50} of approximately 3 days under continuous irradiation and 4.5 days in sunlight-equivalent days), the dissipation of indoxacarb from the water column in water/sediment systems was even more rapid (DT_{50} of 0.5-1.0 days). The rapid partitioning behaviour was expected since the average K_{oc} of indoxacarb was 5125 mL/g. The rapid partitioning into sediment would greatly decrease the amount of indoxacarb in the water column of a natural water body that would be available to undergo photolytic decomposition.

Figure 2.8.2-1
Proposed degradation pathway for indoxacarb in irradiated and non-irradiated buffers

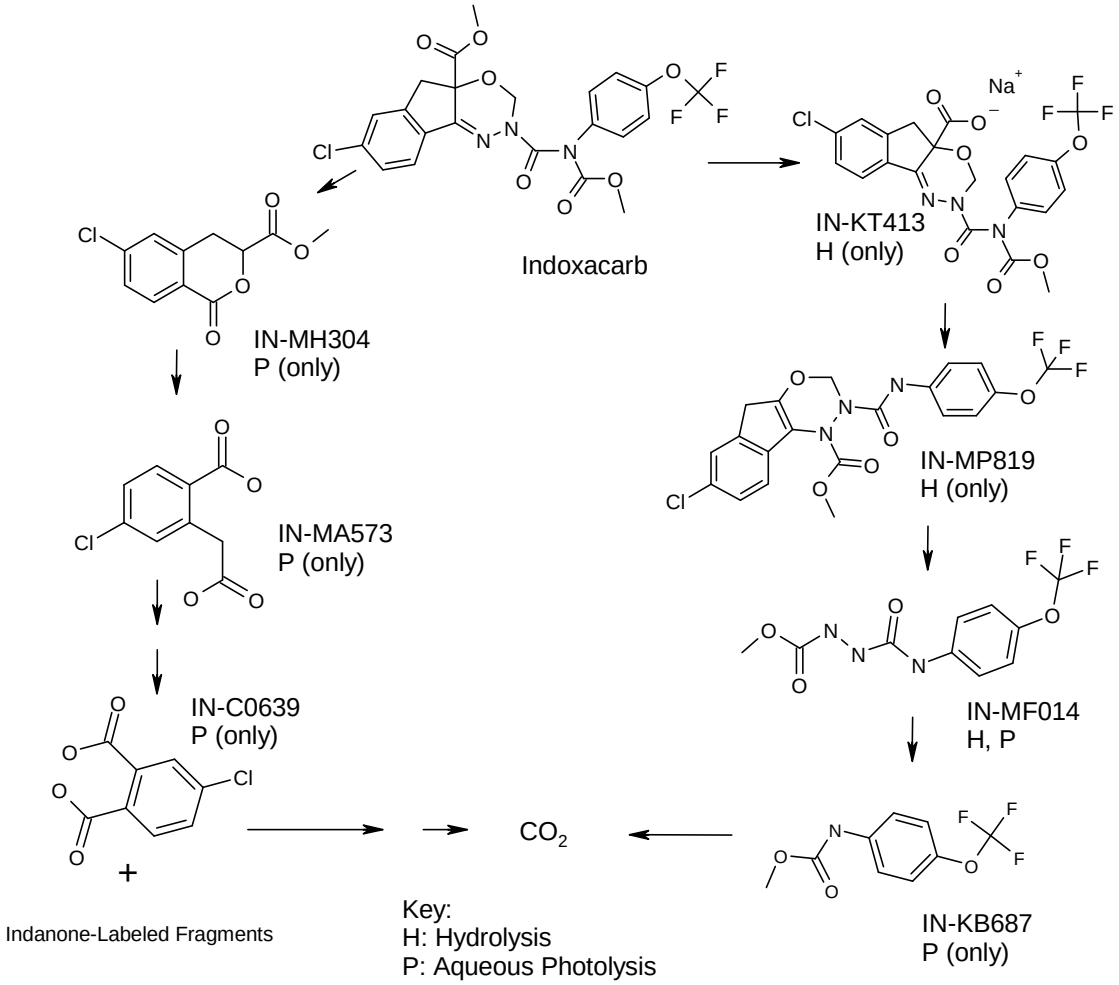
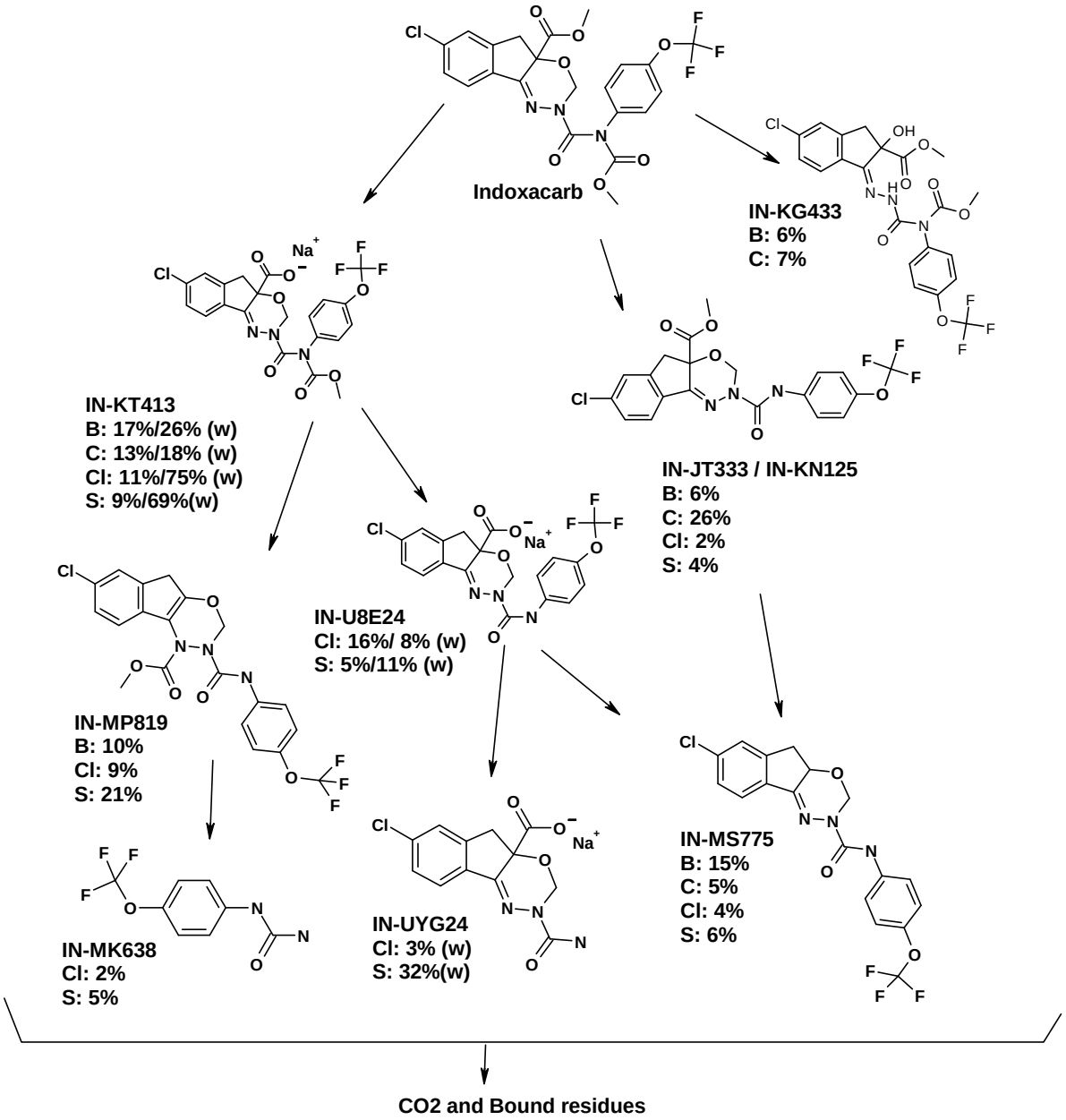


Figure 2.8.2-2
Proposed major degradation pathway for indoxacarb in water/sediment systems



Note:
B: Bury Pond Sediment
C: Chatsworth Sediment
Cl: Clay Loam (Goose River) sediment
S: Sand (Chula) Sediment
(w): the residue percentage with (w) represents that the residue is from water phase. For example, B: 17%/26%(w) indicates that 17% residue is from Bury Pond Sediment and 26% residue is from water phase
Minor metabolites (<5% AR in total system, IN-ML438 and IN-U8F52) were not shown in this proposed major degradation pathway

2.8.3. Summary of fate and behaviour in air

Neither indoxacarb (DPX-KN128) nor any of its principal degradation products have significant volatility. The vapour pressure of indoxacarb has been measured at 9.8×10^{-9} Pa at 20°C. The

Henry's law constant for indoxacarb has been calculated as 6×10^{-5} Pa -m^3/mol at 25°C. The Henry's law constant for indoxacarb is lower than the Henry's law constant for water (3×10^{-2} Pa -m^3/mol). Thus, indoxacarb can be considered to be non-volatile.

Since indoxacarb (DPX-KN128) and its metabolites are considered to be non-volatile, the transport via air of indoxacarb and its metabolites should not be expected as a meaningful pathway in environments, and thus no study has been conducted for this purpose.

2.8.4. Summary of monitoring data concerning fate and behaviour of the active substance, metabolites, degradation and reaction products

No data were submitted. Monitoring studies with indoxacarb (DPX-KN128) were not conducted. The environmental characteristics of indoxacarb are such that monitoring studies would provide little, if any, useful information. Indoxacarb is strongly sorbed to soil and there is little likelihood that it could leach through the soil profile as demonstrated from the field dissipation studies. If it were to enter the aquatic environment, it would rapidly degrade prior to or after partitioning into sediment.

2.8.5. Definition of the residues in the environment requiring further assessment

The following residue definition for risk assessment is proposed:

Soil: Indoxacarb, IN-JT333, IN-KG433, IN-KT413, IN-JU873, IN-ML438, IN-MK638, IN-KB687, IN-MK643, and IN-U8E24.

Groundwater: Indoxacarb, IN-JT333, IN-KG433, IN-KT413, IN-JU873, IN-ML438, IN-MK638, IN-KB687, IN-MK643, and IN-U8E24.

Surface water: Indoxacarb, IN-JT333, IN-KG433, IN-KT413, IN-JU873, IN-ML438, IN-MK638, IN-KB687, IN-MK643, IN-MP819, IN-MS775, IN-U8E24, and IN-UYG24.

Sediment: Indoxacarb, IN-JT333, IN-KG433, IN-KT413, IN-ML438, IN-MP819, and IN-MS775.

Air: Indoxacarb

2.8.6. Summary of exposure calculations and product assessment

Soil

$PECs_{soil}$ were calculated for indoxacarb and its major or minor non-transient soil metabolites IN-JT333, IN-JU873, IN-ML438, IN-KG433, IN-MK643, IN-MK638, IN-KT413 and IN-KB687.

The following DT_{50} were selected for calculation

Compound	DT_{50}	Comments
Indoxacarb	231	Worst case non-normalised (laboratory n = 5), based on DFOP k2 parameter.
IN-JT333	147.5	Worst case non-normalised (laboratory n = 10), based on DFOP k2 parameter.
IN-JU873	103.5	Worst case non-normalised (laboratory n = 5), based on DFOP k2 parameter.
IN-ML438	186.5	Worst case non-normalised (laboratory n = 6), based on DFOP k2 parameter.
IN-KG433	17.4	Worst case non-normalised (laboratory n = 5), based on FOMC DT_{90}/3.32 parameter.
IN-MK643	314.2	Worst case non-normalised (laboratory n = 5), SFO
IN-MK638	17.3	Worst case non-normalised (laboratory n = 5), SFO
IN-KT413	10.34	Worst case non-normalised (laboratory n = 3), based on DFOP k2 parameter.
IN-KB687	0.67[b]	Worst case non-normalised (laboratory n = 2), SFO
IN-U8E24	1000	Default worst-case value

All PECsoil were calculated using standard equation from FOCUS (1997) and default soil depth of 5 cm and bulk density of 1.5 $g.cm^{-3}$.

For Indoxacarb, as worst-case, cumulated multiple applications according to the GAP were considered (i.e. no degradation between applications considered). For all metabolites, pseudo application of metabolite was considered with parent applied dose corrected with maximum occurrence and molar ratio. As a worst-case, a single cumulated application dose of parent active substance was also considered.

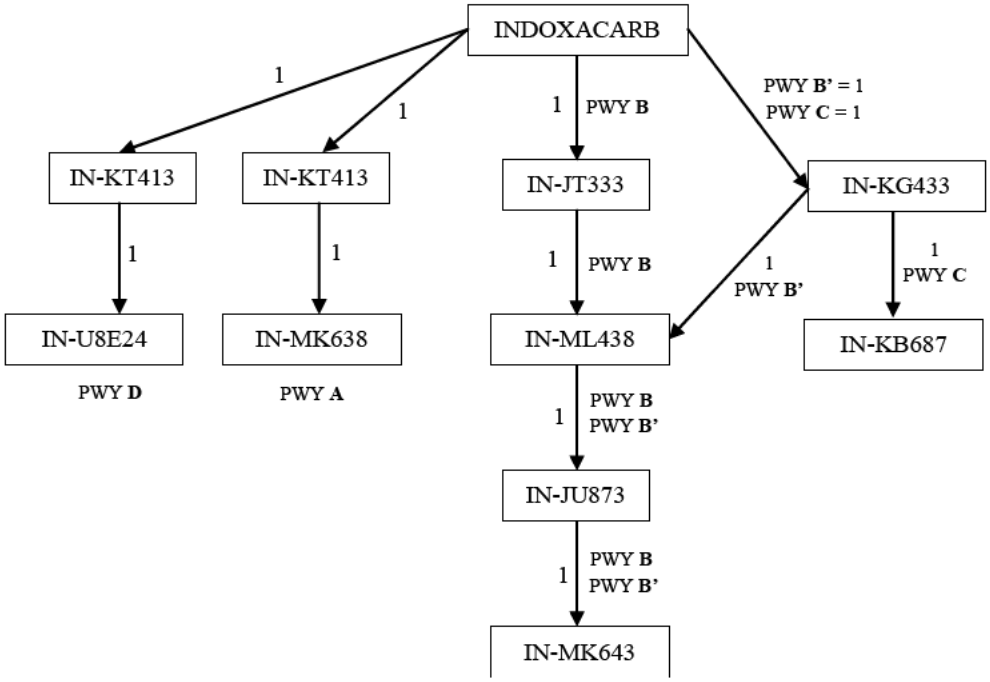
PECplateau calculation was triggered and provided for Indoxacarb, IN-JT333, IN-JU873, IN-ML438, IN-MK643 and IN-U8E24.

The complete PECsoil calculations are presented in Volume_3CP_INDOXACARB 150 EC_B-8 and worst-case values used for risk assessment are presented hereunder in Level 2 section 2.9.9.

Groundwater

The models FOCUS-PEARL 4.4.4 and FOCUS-PELMO 5.5.3 were used to simulate the leaching behaviour of indoxacarb and its major or minor non-transient soil metabolites IN-JT333, IN-JU873, IN-ML438, IN-KG433, IN-MK643, IN-MK638, IN-KT413 and IN-KB687. PECgw calculations were performed for each representative use considering all FOCUS groundwater scenarios that are parameterized for cabbage (surrogate for lettuce) and maize. Crop interception values were chosen according to the guidance of the FOCUS groundwater work group. Applications were considered to start at the earliest growth stage covered by the GAP.

The metabolites were simulated simultaneously with the parent, in 5 different pathways, since default ffm of 1 were systematically used for every metabolite (no reliable fit obtained from parent-metabolite fits). The following degradation scheme was used:



The following main input parameters were used:

	DT_{50} [days]	Ffm from indoxacarb	Kfoc [mL/g]	1/n
Indoxacarb	39.9	-	5125	1
IN-JT333	16.4	1	17300	1
IN-JU873	32.1	1	13167	0.99
IN-ML438	73.7	1	19601	1
IN-KG433	4.2	1	314	0.92
IN-MK643	169.5	1	269	0.81
IN-MK638	8.7	1	151	0.84
IN-KT413	1.7	1	344	0.95
IN-KB687	0.67	1	237	0.85
IN-U8E24	141	1	1910	0.9

PECgw for indoxacarb and all its soil metabolites are <0.1µg/L for all representative uses (<0.001 µg/L).

The complete PECgw calculations are presented in Volume_3CP_INDOXACARB 150 EC_B-8

Surface water

The calculations for PEC in surface water (PEC_{sw}) and sediment (PEC_{sed}) were performed according to the recommendations of the FOCUS working group on surface water scenarios in a stepwise approach considering spray drift, drainage and runoff.

The calculations were made for indoxacarb and for its soil metabolites IN-JT333, IN-KG433, IN-KT413, IN-JU873, IN-ML438, IN-MK638, IN-KB687, IN-MK643, IN-MP819, and for the water/sediment metabolites IN-MS775, IN-U8E24, and IN-UYG24.

The following model versions were used: STEPS1-2 (version 2.1) for Step 1 and Step 2 and SWASH 3.1 in combination with MACRO 4.4.2, PRZM 3.1.1, TOXSWA 3.3.1 and SWAN 3.1.1 for Step 3&4 calculations.

PECsw calculations were performed for each representative use considering all FOCUS surface water scenarios that are parameterized for Lettuce (cabbage for surrogate) and maize. Early and late application stages were considered when necessary and both single and multiple applications were simulated.

For indoxacarb and all metabolites, as it was not possible to fit reliable kinetics to derive individual degradation rates in water and sediment at level P-II or M-II, only whole-system $DegT_{50}$ values were used in PECcalculation. The following DT_{50} values were considered (in addition to the input parameters detailed above for PECgw):

	STEP	DT_{50} in water compartment	DT_{50} in sediment compartment
Indoxacarb	3&4	1000	5.8
IN-JT333	3	1000	66.2
IN-JU873	1&2	1000	1000
IN-ML438	1&2	213.1	213.1
IN-KG433	1&2	1000	1000
IN-MK643	1&2	1000	1000
IN-MK638	1&2	1000	1000
IN-KT413	1&2	28.2	28.2
IN-MP819	1&2	1000	1000
IN-MS775	1&2	1000	1000
IN-KB687	1&2	1000	1000
IN-U8E24	1&2	393.2	393.2
IN-UYG24	1&2	118.7	118.7

For indoxacarb, calculations were done up to Step 4 including mitigation measures (10m of vegetated non-spray buffer zone for maize, and 20m of vegetated non-spray buffer zone for lettuce).
For metabolite IN-JT333, calculations were done up to Step 3. For all others soil or water/sediment metabolite, calculations were performed up to step 1-2.

The complete PECsw calculations are presented in Volume_3CP_INDOXACARB 150 EC_B-8

The worst-case PECsw used for risk assessment are presented hereunder in Level 2 section 2.9.9.

Air

The low vapour pressure (9.8×10^{-9} Pa at 20°C) of indoxacarb indicate a negligible potential for volatilisation of the active substance from soil under practical conditions of use.

2.9. EFFECTS ON NON-TARGET SPECIES

2.9.1. Summary of effects on birds and other terrestrial vertebrates

Avian toxicity endpoints used in risk assessment for indoxacarb and its metabolites

Study	Test substance	Test species	Endpoints	Endpoints used in risk assessment
Acute toxicity	DPX-MP062 technical	Northern Bobwhite	LD_{50} = 98 mg DPX-MP062/kg bw	LD_{50} = 73.5 mg DPX-KN128/kg bw
Acute toxicity	IN-JT333	Northern Bobwhite	LD_{50} = 1750 mg IN-JT333/kg bw	LD_{50} = 1750 mg IN-JT333/kg bw
Acute toxicity	Indoxacarb 150 g/L EC	Northern Bobwhite	-	LD_{50} = 89 mg DPX-KN128/kg bw[a]
Dietary toxicity (short-term)	DPX-MP062 technical	Northern Bobwhite	LD_{50} = 340 mg DPX-MP062/kg bw/d	-
Reproductive toxicity (long-term)	DPX-MP062 technical	Northern Bobwhite	NOEL = 75.7 mg DPX-MP062/kg bw/d	NOEL = 7.35 mg DPX-KN128/kg bw/d (LD_{50}/10)

[a] Summarised in Volume 3_CA_B9

Mammalian toxicity endpoints of indoxacarb

Study	Test substance	Test species	Endpoints	Reference
Acute toxicity	DPX-KN128 technical	Rat	LD_{50} = 843 mg/kg bw (males) LD_{50} = 179 mg/kg bw (females)[a]	HLO-1997-00055[a]
Acute toxicity	Indoxacarb 150 g/L EC	Rat	LD_{50} = 976.8 mg product/kg bw (LD_{50} = 146.4 mg DPX-KN128 /kg bw)[a]	DuPont-13455[a]
Acute toxicity	IN-JT333	Rat	LD_{50} = 52 mg/kg bw (males) LD_{50} = 39 mg/kg bw (females)	HLR 927-96[a]
Reproductive toxicity (long-term)	DPX-JW062[b]	Rat	NOAEL = 1.2 mg DPX-JW062 /kg bw/d[b]	HLO 115-96, Revision No. 1[a]
			Applicant proposal: NOAEL = 4.6 mg DPX-KN128 /kg bw/d[c] RMS proposal: NOAEL = 0.68 mg DPX-KN128 /kg bw/d	

[a] Summarised in section Toxicology.

[b] DPX-JW062 is a racemic mixture of DPX-KN128 and DPX-KN127

[c] Proposed for ecotoxicological risk assessment.

2.9.2. Summary of effects on aquatic organisms

Ecotoxicological endpoints for aquatic species

Group	Test substance	Time-scale (Test type)	End point	Toxicity[1]
Laboratory tests				
Fish				
Oncorhynchus mykiss	DPX-KN128	Acute 96 hr (flow-through)	Mortality, LC_{50}	>0.17 mg a.s./L (mm)
Lepomis macrochirus	DPX-MP062 (79:21 mixture DPX-KN128/IN-KN127)	Acute 96 hr (flow-through)	Mortality, LC_{50}	0.90 mg DPX-MP062/L (mm)
Oncorhynchus mykiss	Indoxacarb 150 g/L EC	Acute 96 hr (static)	Mortality, LC_{50}	7 mg prep./L (0.84 mg a.s./L) (nom)
Pimephales promelas	DPX-KN128	Chronic 28 days (flow-through)	NOEC (ELS)	0.0675 mg/L (mm)
Oncorhynchus mykiss	DPX-MP062 (79:21 mixture DPX-KN128/IN-KN127)	Chronic 90 days (flow-through)	NOEC (ELS)	0.15 mg DPX-MP062/L (mm)
Pimephales promelas	IN-JT333	Chronic 28 days (flow-through)	NOEC (ELS) EC10	0.00242 mg/L (mm) 0.00249 mg/L (mm)
Oncorhynchus mykiss	IN-JT333	96 hr (flow-through)	Mortality, LC_{50}	0.029 mg/L (mm)
Oncorhynchus mykiss	IN-KN124	96 hr (semi-static)	Mortality, LC_{50}	>0.0931 mg/L (mm)
Oncorhynchus mykiss	IN-KN125	96 hr (semi-static)	Mortality, LC_{50}	0.0105 mg/L (mm)
Oncorhynchus mykiss	IN-JU873	96 hr (semi-static)	Mortality, LC_{50}	>0.441 mg/L (mm)
Oncorhynchus mykiss	IN-KG433	96 hr (flow-through)	Mortality, LC_{50}	>0.22 mg/L (mm)
Oncorhynchus mykiss	IN-KT413	96 hr (static)	Mortality, LC_{50}	>1.06 mg/L (mm)
Oncorhynchus mykiss	IN-MK638	96 hr (static)	Mortality, LC_{50}	28 mg/L (mm)
Oncorhynchus mykiss	IN-MK643	96 hr (static)	Mortality, LC_{50}	6.99 mg/L (mm)
Oncorhynchus mykiss	IN-KB687	96 hr (static)	Mortality, LC_{50}	11.9 mg/L (mm)
Oncorhynchus mykiss	IN-MP819	96 hr (flow-through)	Mortality, LC_{50}	>0.368 mg/L (mm)
Oncorhynchus mykiss	IN-MS775	96 hr (static)	Mortality, LC_{50}	>0.00396 mg/L (mm)
Oncorhynchus mykiss	IN-U8E24	96 hr (static)	Mortality, LC_{50}	46.5 mg/L (mm)

Oncorhynchus mykiss	IN-UYG24	96 hr (static)	Mortality, LC_{50}	>115 mg/L (mm)
Aquatic invertebrates				
Daphnia magna	DPX-KN128	48 h (flow-through)	Mortality, EC_{50}	>0.17 mg/L (mm)
Mysidopsis bahia	DPX-KN128	96 h (flow-through)	Mortality, EC_{50}	>0.126 mg/L (mm)
Daphnia magna	Indoxacarb 150 g/L EC	48 h (static)	Mortality, EC_{50}	1.38 prod./L (0.22 mg a.s./L) (ini)
Mysidopsis bahia	Indoxacarb 150 g/L EC	96 hr (static)	Mortality, LC_{50}	5.0 mg prep./L (0.75 mg a.s./L) (ini)
Daphnia magna	DPX-KN128	21 d (semi-static)	Reproduction and development, NOEC	0.0351 mg/L (mm)
Mysidopsis bahia	DPX-MP062 (79:21 mixture DPX-KN128/IN-KN127)	28 days (flow-through)	Reproduction and development, NOEC	0.0184 mg DPX-MP062/L (mm) (equivalent to 0.0145 mg DPX-KN128/L)
Daphnia magna	IN-KT413	21 d (semi-static)	Reproduction and development, NOEC	3.9 mg/L (mm)
Daphnia magna	IN-JT333	48 h (semi-static)	Mortality, EC_{50}	>0.029 mg/L (mm)
Mysidopsis bahia	IN-JT333	96 h (semi-static)	Mortality, EC_{50}	0.07 mg/L (mm)
Daphnia magna	IN-KN124	48 h (semi-static)	Mortality, EC_{50}	>0.106 mg/L (mm)
Daphnia magna	IN-KN125	48 h (semi-static)	Mortality, EC_{50}	>0.121 mg/L (mm)
Daphnia magna	IN-JU873	48 h (semi-static)	Mortality, EC_{50}	0.379 mg/L (mm)
Mysidopsis bahia	IN-JU873	96 h (semi-static)	Mortality, EC_{50}	>1.47 mg/L (mm)
Daphnia magna	IN-KG433	48 h (static)	Mortality, EC_{50}	>0.23 mg/L (mm)
Daphnia magna	IN-KT413	48 h (static)	Mortality, EC_{50}	>0.967 mg/L (mm)
Mysidopsis bahia	IN-KT413	96 h (static)	Mortality, EC_{50}	2.8 mg/L (mm)
Daphnia magna	IN-MK638	48 h (static)	Mortality, EC_{50}	80 mg/L (mm)
Mysidopsis bahia	IN-MK638	96 h (static)	Mortality, EC_{50}	41.1 mg/L (mm)
Daphnia magna	IN-MK643	48 h (static)	Mortality, EC_{50}	34.1 mg/L (mm)
Mysidopsis bahia	IN-MK643	96 h (static)	Mortality, EC_{50}	16.4 mg/L (mm)
Daphnia magna	IN-KB687	48 h (static)	Mortality, EC_{50}	7.83 mg/L (mm)

Mysidopsis bahia	IN-KB687	96 h (semi-static)	Mortality, EC_{50}	7.2 mg/L (mm)
Daphnia magna	IN-MP819	48 h (flow-through)	Mortality, EC_{50}	0.06 mg/L (mm)
Daphnia magna	IN-MS775	48 h (static)	Mortality, EC_{50}	>0.00567 mg/L (mm)
Daphnia magna	IN-U8E24	48 h (static)	Mortality, EC_{50}	>12 mg/L (nom)
Daphnia magna	IN-UYG24	48 h (static)	Mortality, EC_{50}	>120 mg/L (nom)
Sediment-dwelling organisms				
Chironomus riparius (spiked water)	DPX-KN128	28 d (static)	EC10	0.00168 mg/L (mm)
Chironomus riparius (spiked water)	DPX-KN128	28 d (static)	NOEC development rate	0.00292 mg a.s./kg dry sediment (mm) 0.0018 mg a.s./L (mm)
Chironomus riparius (spiked water)	IN-KT413	28 d (static)	NOEC development rate EC10 (development time)	0.024 mg/L (mm) 0.088 mg/L (mm)
Chironomus riparius (spiked sediment)	IN-JT333	28 d (static)	NOEC development rate	0.096 mg/kg dry sediment (mm)
Chironomus riparius (spiked sediment)	IN-KG433	28 d (static)	NOEC emergence ratio	0.17 mg/kg dry sediment (ini)
Chironomus riparius (spiked sediment)	IN-KT413	28 d (static)	NOEC development rate	7.5 mg/kg dry sediment (mm)
Chironomus riparius (spiked sediment)	IN-MP819	28 d (static)	NOEC emergence, development rate	86.2 mg/kg dry sediment (mm)
Chironomus riparius (spiked sediment)	IN-MS775	28 d (static)	NOEC emergence ratio	2.2 mg/kg dry sediment (mm)
Algae				
Pseudokirchneriella subcapitata	DPX-KN128	72/96 h (static)	Growth rate: 72 h E_rC_{50} NOECr Biomass: 72 h E_bC_{50} NOECb Yield: 72 h E_yC_{50} NOECy	>0.0793 mg/L (mm) 0.0793 mg/L (mm) >0.0793 mg/L (mm) 0.0793 mg/L (mm) >0.0793 mg/L (mm) 0.0793 mg/L (mm)
Pseudokirchneriella subcapitata	Indoxacarb 150 g/L EC	72 h (static)	Growth rate: 72 h E_rC_{50} NOECr Biomass: 72 h E_bC_{50} NOECb	>16 mg/L (nom) 1.8 mg/L (nom) 12.5 mg/L (nom) 1.8 mg/L (nom)

Pseudokirchneriella subcapitata	IN-JT333	72/96/120 h (static)	Growth rate: 72 h E_rC_{50} NOECr Biomass: 72 h E_bC_{50} NOECb	>0.0075 mg/L (mm) 0.0075 mg/L (mm) >0.0075 mg/L (mm) 0.0075 mg/L (mm)
Pseudokirchneriella subcapitata	IN-KN124	72/96 h (static)	Growth rate: 72 h E_rC_{50} NOECr Biomass: 72 h E_bC_{50} NOECb Yield: 72 h E_yC_{50} NOECy	>0.0478 mg/L (mm) 0.0478 mg/L (mm) >0.0478 mg/L (mm) 0.0478 mg/L (mm) >0.0478 mg/L (mm) 0.0478 mg/L (mm)
Pseudokirchneriella subcapitata	IN-KN125	72/96 h (static)	Growth rate: 72 h E_rC_{50} NOECr Biomass: 72 h E_bC_{50} NOECb Yield: 72 h E_yC_{50} NOECy	>0.0508 mg/L (mm) 0.0508 mg/L (mm) >0.0508 mg/L (mm) 0.0508 mg/L (mm) >0.0508 mg/L (mm) 0.0508 mg/L (mm)
Pseudokirchneriella subcapitata	IN-JU873	72 h (static)	Growth rate: 72 h E_rC_{50} NOECr Biomass: 72 h E_bC_{50} NOECb Yield: 72 h E_yC_{50} NOECy	>0.265 mg/L (mm) 0.0332 mg/L (mm) >0.265 mg/L (mm) 0.0332 mg/L (mm) >0.265 mg/L (mm) 0.0332 mg/L (mm)
Pseudokirchneriella subcapitata	IN-KT413	72 h (static)	Growth rate: 72 h E_rC_{50}	>105 mg/L (mm)
Pseudokirchneriella subcapitata	IN-MK638	72 h (static)	Growth rate: 72 h E_rC_{50} NOECr Biomass: 72 h E_bC_{50} NOECb Yield: 72 h E_yC_{50} NOECy	37.2 mg/L (mm) 0.641 mg/L (mm) 7.55 mg/L (mm) 0.641 mg/L (mm) 7.45 mg/L (mm) 0.641 mg/L (mm)

Pseudokirchneriella subcapitata	IN-MK643	72 h (static)	Growth rate: 72 h E_rC_{50} NOECr Biomass: 72 h E_bC_{50} NOECb Yield: 72 h E_yC_{50} NOECy	59.7 mg/L (mm) 3.40 mg/L (mm) 31.8 mg/L (mm) 3.40 mg/L (mm) 31.8 mg/L (mm) 3.40 mg/L (mm)
Pseudokirchneriella subcapitata	IN-KB687	72 h (static)	Growth rate: 72 h E_rC_{50} NOECr Biomass: 72 h E_bC_{50} NOECb Yield: 72 h E_yC_{50} NOECy	>2.26 mg/L (mm) 0.0679 mg/L (mm) 1.41 mg/L (mm) 0.0227 mg/L (mm) 1.39 mg/L (mm) 0.0227 mg/L (mm)
Pseudokirchneriella subcapitata	IN-MP819	72 h (static)	Growth rate: 72 h E_rC_{50} NOECr Biomass: 72 h E_bC_{50} NOECb Yield: 72 h E_yC_{50} NOECy	>0.358 mg/L (mm) 0.358 mg/L (mm) >0.358 mg/L (mm) 0.358 mg/L (mm) >0.358 mg/L (mm) 0.358 mg/L (mm)
Pseudokirchneriella subcapitata	IN-MS775	72 h (static)	Growth rate: 72 h E_rC_{50} NOECr Biomass: 72 h E_bC_{50} NOECb Yield: 72 h E_yC_{50} NOECy	>0.052 mg/L (mm) 0.052 mg/L (mm) >0.052 mg/L (mm) 0.052 mg/L (mm) >0.052 mg/L (mm) 0.052 mg/L (mm)
Pseudokirchneriella subcapitata	IN-U8E24	72/96 h (static)	Growth rate: 72 h E_rC_{50} NOECr Biomass: 72 h E_bC_{50} NOECb Yield: 72 h E_yC_{50} NOECy	55.2 mg/L (mm) 6.1 mg/L (mm) 31.3 mg/L (mm) 6.1 mg/L (mm) 32.6 mg/L (mm) 6.1 mg/L (mm)
Pseudokirchneriella subcapitata	IN-UYG24	72/96 h (static)	Growth rate: 72 h E_rC_{50} NOECr Biomass: 72 h E_bC_{50} NOECb Yield: 72 h E_yC_{50} NOECy	>106 mg/L (mm) 27.4 mg/L (mm) 74.5 mg/L (mm) 6.64 mg/L (mm) 73.0 mg/L (mm) 6.64 mg/L (mm)

[1] (nom) nominal concentration; (mm) mean measured concentration; (ini) initial measured concentration; prep.: preparation; a.s.: active substance

2.9.3. Summary of effects on arthropods

Ecotoxicological endpoints for honey bees and bumblebees

Species	Test substance	Type	Dose	Endpoint/observation	Reference
Laboratory testing					
Honey bee	Indoxacarb 150 g/L EC	48 h oral LD_{50}	-	0.11 µg a.s./bee, (0.69 µg prod./bee)	DuPont-18924[b]
		48 h contact LD_{50}	-	0.08 µg a.s./bee (0.50 µg prod./bee)	
Honey bee	Indoxacarb technical (DPX-KN128)	48 h oral LD_{50}		0.232 µg a.s./bee	DuPont-36500[a]
		48 h contact LD_{50}		0.0682 µg a.s./bee	
Bumble bee	Indoxacarb 150 g/L EC	96 h oral LD_{50}	-	0.11 µg a.s./bee, (0.73 µg prod./bee)	DuPont-38351[b]
		96 h contact LD_{50}	-	0.32 µg a.s./bee (2.13 µg prod./bee)	
Bumble bee	Indoxacarb technical (DPX-KN128)	96 h oral LD_{50}	-	0.07 µg a.s./bee	DuPont-38350[a]
		96 h contact LD_{50}	-	0.25 µg a.s./bee	
Honey bee	Indoxacarb technical (DPX-KN128)	10 d chronic LD_{50} oral	-	0.0649 µg a.s./bee/day	DuPont-36490[a]
Honey bee	Indoxacarb 150 g/L EC	10 d chronic LD_{50} oral	-	0.0399 µg a.s./bee/day (0.266 µg prod./bee)	DuPont-36492[b]
Honey bee	Indoxacarb 150 g/L EC	7 d lab larvae NOED	-	1.11 µg a.s./bee (7.4 µg prod./bee)	DuPont-34817[b]
Oomen Brood feeding testing					
Honey bee	Indoxacarb technical (DPX-KN128)	Bee brood feeding study	100 µg a.s./kg	Effects on mortality. Brood index and termination rate of eggs and young larvae were affected	DuPont-36493[a]
Honey bee	Indoxacarb technical (DPX-KN128)	Bee brood feeding study	100 µg a.s./kg	No adverse effects on any parameter tested.	DuPont-43111[a]
Honey bee	Indoxacarb 150 g/L EC	Bee brood feeding study	100 µg a.s./kg 667 µg prod./kg	No adverse effects on any parameter tested.	DuPont-37488[b]
Semi-field testing					
Honey bee colonies	Indoxacarb 150 g/L EC	Bee brood study on flowering *Phacelia tanacetifolia* in Germany	50 g a.s./ha 333 g prod./ha	Transient effect on flight activity, behaviour and mortality Strong effect on the brood development No effect on colony size, pupal mortality	DuPont-34108[b]

Honey bee colonies	Indoxacarb 150 g/L EC	Semi-field study on *Phacelia tanacetifolia* in Germany	55.5 g a.s./ha 370 mL prod./ha during bee flight	No harmful effects on honey bee mortality in 2 of the 3 tunnels, transient mortality in 1 tunnel. No harmful effects on flight intensity, brood development, and behaviour	DuPont-19449 [b]
Honey bee colonies	Indoxacarb 150 g/L EC	Semi-field study on *Phacelia tanacetifolia* in France	55.6 g a.s./ha 371 mL prod./ha during bee flight	No harmful effects on flight intensity and brood development, increased mortality at day of application and 1 day thereafter	DuPont-19450 [b]
Honey bee colonies	Indoxacarb 150 g/L EC	Semi-field study on *Phacelia tanacetifolia* in Germany	55.6 g a.s./ha 359 mL prod./ha during bee flight	No harmful effects on brood development, increased mortality at day of application and 1 day thereafter Transient effects on flight intensity and behaviour	DuPont-19451 [b]
Honey bee colonies	Indoxacarb 150 g/L EC	Semi-field study on flowering *Phacelia tanacetifolia* in Germany	37.5 g a.s./ha 250 mL prod./ha <u>during</u> bee flight 37.5 g a.s./ha 250 mL prod./ha <u>after</u> bee flight	<u>During bee flight:</u> Transient increase in mortality (up to DAA2) when applied during daily bee flight. No effect on colony strength and brood development. Slight effect on flight intensity and behaviour when applied during daily bee flight. <u>After bee flight:</u> No effect on mortality, flight intensity, colony strength and brood development when applied in evening after daily bee flight. Slight and transient effect on behaviour when applied in evening after daily bee flight.	DuPont-36482 [b]

Honey bee colonies	Indoxacarb 150 g/L EC	Semi-field study on flowering *Phacelia tanacetifolia* in Germany	50 g a.s./ha 333 mL prod./ha <u>after</u> bee flight	Transient effect on mortality (up to DAA3), and on flight intensity (day after application) and behaviour. No effect on colony size but slight and transient effect on the amount of brood cells after treatment. Obvious effects on brood development, particularly on the eggs.	DuPont-38405 [b]
Honey bee colonies	Indoxacarb 150 g/L EC	Semi-field study on flowering *Phacelia tanacetifolia* in Germany	37.5 g a.s./ha 250 mL prod./ha <u>during</u> bee flight 37.5 g a.s./ha 250 mL prod./ha <u>after</u> bee flight	<u>During bee flight:</u> Increase of pupal mortality when applied during daily bee flight. Slight and transient effect on flight intensity and behaviour. No adverse effect on mortality and colony size when applied during daily bee flight. Slight effect on the amount of brood. Obvious effects on the brood development (eggs and larvae). <u>After bee flight:</u> Slight and transient effect on flight intensity and behaviour when applied after daily bee flight. No adverse effect on mortality and colony size when applied after daily bee flight.. Possible effect on the amount of brood. Obvious effects on the brood development (eggs and larvae).	DuPont-37489, Revision No. 1 [b]
Honey bee colonies	Indoxacarb 150 g/L EC	Semi-field study on *Phacelia tanacetifolia* in France	50 g a.s./ha 333 mL prod./ha <u>during</u> bee flight	<u>During bee flight:</u> Transient effects on mortality and foraging activity were observed when applied during daily bee flight.	DuPont-19453 [b]

			50 g a.s./ha 333 mL prod./ha <u>after</u> bee flight	<u>After bee flight:</u> No harmful effects on honey bee mortality, foraging activity when applied after daily bee flight.	
Honey bee colonies	Indoxacarb 150 g/L EC	Semi-field study on *Phacelia tanacetifolia* in France	55.6 g a.s./ha 371 mL prod./ha <u>during</u> bee flight 55.6 g a.s./ha 371 mL prod./ha <u>after</u> bee flight	Increase of mortality on day of application when applied during flight. Effects on foraging during 4 days. <u>After bee flight:</u> Results considered not fully reliable.	DuPont-21945 [b]
Honey bee colonies	Indoxacarb 150 g/L EC	Semi-field study on flowering maize in Germany	37.5 g a.s./ha 250 mL prod./ha <u>during</u> bee flight 37.5 g a.s./ha 250 mL prod./ha <u>after</u> bee flight	<u>During bee flight:</u> Increase in honey bee mortality when applied during flight (up to 3 DAA). No effect on honey bee flight activity, brood development and colony condition. Effects on behaviour. <u>After bee flight:</u> Slight increase in honey bee mortality when applied after flight (0DAA). No effect on honey bee flight activity, brood development and colony condition. Effects on behaviour.	DuPont-37487 [b]
Honey bee colonies	Indoxacarb 150 g/L EC	Semi-field study on flowering *Phacelia tanacetifolia* in Germany	37.5 g a.s./ha 232.1 mL prod./ha <u>during</u> bee flight 37.5 g a.s./ha 232.1 mL prod./ha <u>after</u> bee flight	Study considered valid but to be used with caution. <u>During bee flight:</u> No effect on mortality, flight intensity, colony strength when applied during flight. Slight and transient effect on behaviour. <u>After bee flight:</u> Slight effect on mortality and behaviour when applied after flight. No effect on flight intensity, colony strength.	DuPont-41668 [b]

Honey bee colonies	Indoxacarb 150 g/L EC	Semi-field study on wheat treated with artificial honeydew in France	55.6 g a.s./ha 375 mL prod./ha <u>during</u> bee flight 55.6 g a.s./ha 375 mL prod./ha 3 hours <u>before</u> bee flight	Study not reliable. Effects on mortality were however obvious.	DuPont-19454[b]
Honey bee colonies	Indoxacarb 150 g/L EC	Semi-field study on wheat treated with artificial honeydew in France	37.5 g a.s./ha 250 mL prod./ha <u>during</u> bee flight 37.5 g a.s./ha 250 mL prod./ha <u>after</u> bee flight	Not reliable for risk assessment.	DuPont-19455[b]
Honey bee colonies	Indoxacarb 150 g/L EC	Semi-field study on wheat treated with artificial honeydew in France	55.6 g a.s./ha 375 mL prod./ha <u>during</u> bee flight 55.6 g a.s./ha 375 mL prod./ha after bee flight	Increase in honey bee mortality and flight intensity up to 5 DAA in both treatments. Mortality was high in both cases.Changes in behaviour noted on the day of application when applied after bee flight and noted up to 2 DAA when applied during bee flight. No larvae was found at the end of the test in both cases.	DuPont-21944[b]
Honey bee colonies	Indoxacarb 150 g/L EC	Semi-field study on oilseed rape in France	50 g a.s./ha during bee flight 50 g a.s./ha after bee flight	<u>During bee flight:</u> Mortality was observed when applied during daily bee flight. No effect on flight activity. <u>After bee flight:</u> No effects on mortality and flight activity when applied after daily bee flight.	Etude No. 92-2006[b]

Bumblebee colonies	Indoxacarb 150 g/L EC	Semi-field study on flowering *Phacelia tanacetifolia* in Germany	37.5 g a.s./ha 249.1 mL prod./ha in 400L water <u>after</u> bumblebee flight	Not considered valid for risk assessment.	DuPont-38419 [b]
Field testing					
Honey bee colonies	Indoxacarb 150 g/L EC	Field study on oilseed rape before flowering (BBCH <59) in Germany, <u>hives exposed from d 9 and d 14 after application</u> <u>Application before flowering</u>	25.5 g a.s./ha 170 mL prod./ha in 300 L water/ha	No harmful effects on honey bee mortality, flight intensity, brood development, and behaviour 9 and 14 days after application; no residue of a.s. in honey	DuPont-26946 [b]
Honey bee colonies	Indoxacarb 150 g/L EC	Field study on flowering oilseed rape (BBCH <61) in Germany, <u>hives exposed from d 4 and d 6 after application</u> <u>Application at the beginning of flowering</u>	25.5 g a.s./ha 170 mL prod./ha	No harmful effects on honey bee mortality, brood development, and behaviour 4 and 6 days after application; no residue of a.s. in honey	DuPont-26947 [b]
Honey bee colonies	Indoxacarb 150 g/L EC	Field study on maize in Germany, colonies exposed in evening after flight <u>Application at the beginning of flowering</u>	37.5 g a.s./ha 250 mL prod./ha in 300 L water/ha	Increase of mortality cannot be excluded. Results on flight intensity inconclusive. No test item related impact on the behaviour, and brood development. Test not representative of an application on a flowering crop.	DuPont-30106 [b]

[a] Summarised in Volume 3_CA

[b] Summarised in Volume 3_CP

Summary of effects of Indoxacarb 150 g/L EC on non-target arthropods

Species	Test (test substance and test rate)	Measurement endpoint	Endpoint value	Reference[a]
Aphidius rhopalosiphi	Laboratory Tier 1 (Indoxacarb 150 g/L EC)	LR_{50}	5.1 g a.s./ha (34 mL product/ha)	DuPont-19443
Aphidius rhopalosiphi	Extended laboratory Tier 2 (Indoxacarb 150 g/L EC)	LR_{50} (Mortality) ER_{50} (Reproduction)	74.2 g a.s./ha (494.7 mL product/ha) ≥52.5 g a.s./ha (≥350 mL product/ha)	DuPont-19445
Aphidius rhopalosiphi	Extended laboratory – aging test (1-4 × 100 g a.s./ha Indoxacarb 150 g/L EC)	Mortality and Reproduction after the 1st, 4th application (bioassay 1 and 2, respectively) and after 28 and 56 d field aging (bioassay 3 and 4, respectively)	Bioassay 1: 97.5% mortality Bioassay 2: 100% mortality Bioassay 3: 13.2% mortality and 57.8% reduction in reproduction Bioassay 4: 2.5% mortality and 37.6% reduction in reproduction	DuPont-21947
Typhlodromus pyri	Laboratory Tier 1 (Indoxacarb 150 g/L EC)	LR_{50}	220.5 g a.s./ha (1470 mL product/ha)	DuPont-19444
Chrysoperla carnea	Extended laboratory Tier 2 (Indoxacarb 150 g/L EC)	LR_{50} Effect on reproduction	29.8 g a.s./ha (198.7 mL product/ha) 37.7% reduction at 6.9 g a.s./ha and 67.4% reduction at 17.25 g a.s./ha	DuPont-19446
Chrysoperla carnea	Extended laboratory – aging test (1-4 × 100 g a.s./ha Indoxacarb 150 g/L EC)	Mortality and Reproduction after the 1st, 4th application (bioassay 1 and 2, respectively) and after 28 field ageing (bioassay 3)	Bioassay 1: not valid Bioassay 2: 94% mortality Bioassay 3: 8.8% mortality and no adverse effect on fecundity and hatching (fertilization) compared to controls	DuPont-21946
Orius laevigatus	Extended laboratory – aging test (1-4 × 100 g a.s./ha Indoxacarb 150 g/L EC)	Mortality and Reproduction after the 1st, 4th application (bioassay 1 and 2, respectively)	Bioassay 1: 22% mortality, and no adverse effect on fecundity and hatching Bioassay 2: 9% mortality, 13.5% reduction in reproduction and 10.2% reduction in hatching	DuPont-22391

[a] Summarised in Volume 3_CP

2.9.4. Summary of effects on non-target soil meso- and macrofauna

Ecotoxicological endpoints for soil macro organisms

Test organism	Test substance	Application method of test a.s./ OM[1]	Time scale	End point	Toxicity
Earthworms					
Eisenia fetida	DPX-KN128	5% peat in test soil, test item mixed into soil	Chronic 56 d	reproduction	56-d NOEC = 29.2 mg/kg dry soil EC10 = 23.95 mg a.s./kg dry soil
Eisenia fetida	Indoxacarb 150 g/L EC	10% peat in test soil, test item mixed into soil	Chronic 56 d	reproduction	56-d NOEC = 199.3 mg product/kg dry soil (29.9 mg a.s./kg dry soil) EC10 = 142.88 mg prep./kg dry soil (21.43 mg a.s./kg dry soil)
Eisenia fetida	IN-JT333	5% peat in test soil, test item mixed into soil	Chronic 56 d	Growth, reproduction, behaviour	56-d NOEC = 100 mg/kg dry soil EC10 = 54.86 mg/kg dry soil
Eisenia fetida	IN-JT333	10% peat in test soil, test item mixed into soil	Chronic 56 d	reproduction	56-d NOEC = 2.5 mg/kg dry soil
Eisenia fetida	IN-JU873	5% peat in test soil, test item mixed into soil	Chronic 56 d	reproduction	56-d NOEC = 50 mg/kg dry soil EC10 = 89.12 mg/kg dry soil
Eisenia fetida	IN-KG433	5% peat in test soil, test item mixed into soil	Chronic 56 d	reproduction	56-d NOEC = 50 mg/kg dry soil EC10 = 55.3 mg/kg dry soil
Eisenia fetida	IN-KT413	5% peat in test soil, test item mixed into soil	Chronic 56 d	Growth, reproduction, behaviour	56-d NOEC = 100 mg/kg dry soil

Eisenia fetida	IN-MK638	5% peat in test soil, test item mixed into soil	Chronic 56 d	Growth	56-d NOEC = 50 mg/kg dry soil
Eisenia fetida	IN-MK643	5% peat in test soil, test item mixed into soil	Chronic 56 d	Growth, reproduction, behaviour	56-d NOEC = 25 mg/kg dry soil EC10 = 22.25 mg/kg dry soil
Eisenia fetida	IN-KB687	5% peat in test soil, test item mixed into soil	Chronic 56 d	reproduction	56-d NOEC = 50 mg/kg dry soil
Other soil macroorganisms					
Folsomia candida	DPX-KN128	5% peat in test soil, test item mixed into soil	Chronic 28 d	reproduction	NOEC = 125 mg/kg dry soil EC10 = 106.8 mg/kg dry soil
Folsomia candida	Indoxacarb 150 g/L EC	5% peat in test soil, test item mixed into soil	Chronic 28 d	reproduction	28-d NOEC = 6.6 mg prep./kg dry soil (1 mg a.s./kg dry soil) EC10 = 14.86 mg prep./kg dry soil
Folsomia candida	IN-JT333	5% peat in test soil, test item mixed into soil	Chronic 28 d	reproduction	NOEC = 50 mg/kg dry soil EC10 = 64.17 mg/kg dry soil
Folsomia candida	IN-JU873	5% peat in test soil, test item mixed into soil	Chronic 28 d	reproduction	NOEC = 100 mg/kg dry soil
Folsomia candida	IN-KG433	5% peat in test soil, test item mixed into soil	Chronic 28 d	reproduction	NOEC = 6.25 mg/kg dry soil
Folsomia candida	IN-KT413	5% peat in test soil, test item mixed into soil	Chronic 28 d	reproduction	NOEC= 100 mg/kg dry soil

Folsomia candida	IN-MK638	5% peat in test soil, test item mixed into soil	Chronic 28 d	reproduction	NOEC= 25 mg/kg dry soil EC10 = 10.15 mg/kg dry soil
Folsomia candida	IN-MK643	10% peat in test soil, test item mixed into soil	Chronic 28 d	reproduction	NOEC= 10 mg/kg dry soil EC10 = 80.28 mg/kg dry soil
Folsomia candida	IN-KB687	5% peat in test soil, test item mixed into soil	Chronic 28 d	reproduction	NOEC= 6.25 mg/kg dry soil EC10 = 10.80 mg/kg dry soil
Hypoaspis aculeifer	DPX-KN128	5% peat in test soil, test item mixed into soil	Chronic 14 d	reproduction	NOEC = 1000 mg/kg dry soil
Hypoaspis aculeifer	Indoxacarb 150 g/L EC	5% peat in test soil, test item mixed into soil	Chronic 14 d	reproduction	NOEC = 95.3 mg prep./kg dry soil (14.3 mg a.s./kg dry soil) EC10 = 137.2 mg prep./kg dry soil
Hypoaspis aculeifer	IN-JT333	5% peat in test soil, test item mixed into soil	Chronic 14 d	reproduction	NOEC = 100 mg/kg dry soil
Hypoaspis aculeifer	IN-JU873	5% peat in test soil, test item mixed into soil	Chronic 14 d	reproduction	NOEC = 100 mg/kg dry soil
Hypoaspis aculeifer	IN-KG433	5% peat in test soil, test item mixed into soil	Chronic 14 d	reproduction	NOEC = 100 mg/kg dry soil
Hypoaspis aculeifer	IN-KT413	5% peat in test soil, test item mixed into soil	Chronic 14 d	reproduction	NOEC = 100 mg/kg dry soil EC10 = 62.7 mg/kg dry soil

Hypoaspis aculeifer	IN-MK638	5% peat in test soil, test item mixed into soil	Chronic 14 d	reproduction	NOEC = 100 mg/kg dry soil
Hypoaspis aculeifer	IN-MK643	5% peat in test soil, test item mixed into soil	Chronic 14 d	reproduction	NOEC = 100 mg/kg dry soil
Hypoaspis aculeifer	IN-KB687	5% peat in test soil, test item mixed into soil	Chronic 14 d	reproduction	NOEC = 3.125 mg/kg dry soil EC10 = 5.44 mg/kg dry soil

2.9.5. Summary of effects on soil nitrogen transformation

Ecotoxicological endpoints for soil nitrogen transformation

Nitrogen transformation	Indoxacarb 150 g/L EC	0.84, 4.17, and 8.35 mg formulated product/kg soil dry weight	<25% effect at day 28 at 8.35 mg formulated product/kg soil dry weight
Nitrogen transformation	DPX-MP062 (79:21 mixture DPX-KN128/IN-KN127)	250 g DPX-MP062/ha	<25% effect at day 28 at 250 g a.s./ha (0.333 mg DPX-MP062/kg soil dry weight).
Nitrogen transformation	IN-JT333	60 g IN-JT333/ha	<25% effect at day 28 at 60 g/ha (0.08 mg IN-JT333/kg soil dry weight).
Nitrogen transformation	IN-JU873	0.087 and 0.87 mg IN-JU873/kg soil dry weight	<25% effect at day 28 at 0.087 and 0.87 mg IN-JU873/kg soil dry weight
Nitrogen transformation	IN-KG433	0.076 mg IN-KG433/kg soil dry weight	<25% effect at day 28 at 0.076 mg IN-KG433/kg soil dry weight (14.87%) based on nitrogen levels 28% effect at day 28 at 0.076 mg IN-KG433/kg soil dry weight based on nitrogen transformation
Nitrogen transformation	IN-KT413	0.102 and 1.02 mg IN-KT413/kg soil dry weight	<25% effect at day 28 at 0.102 and 1.02 mg IN-KT413/kg soil dry weight
Nitrogen transformation	IN-MK638	0.042 and 0.42 mg IN-MK638/kg soil dry weight	<25% effect at day 28 at 0.042 and 0.42 mg IN-MK638/kg soil dry weight

Nitrogen transformation	IN-MK643	0.041 and 0.41 mg IN-MK643/kg soil dry weight	<25% effect at day 28 at 0.041 and 0.41 mg IN-MK643/kg soil dry weight
Nitrogen transformation	IN-KB687	0.13, 0.67, and 1.33 mg/kg soil dry weight	<25% effect at day 28 at up to 1.33 mg IN-KB687/kg soil dry weight

2.9.6. Summary of effects on terrestrial non-target higher plants

Species	Test substance	ER_{50} $(g/ha)^2$ vegetative vigour	ER_{50} $(g/ha)^2$ emergence
Zea mays (corn) *Avena sativa* (oat) *Allium cepa* (common onion) *Lolium perenne*, (perennial ryegrass) *Cucumis sativa* (cucumber) *Brassica napus*, (oilseed rape) *Pisum sativum* (pea) *Glycine max* (soybean) *Beta vulgaris* (sugar beet) *Lycopersicon esculentum* (tomato)	Indoxacarb 150 g/L EC	> 100 g a.s./ha	-
Allium cepa (common onion) *Triticum aestivum* (wheat) *Sorghum bicolour* (sorghum) *Zea mays* (corn) *Beta vulgaris* (sugarbeet) *Brassica napus* (oilseed rape) *Cucumis sativa* (cucumber) *Glycine max* (soybean) *Lycopersicon esculentum* (tomato) *Pisum sativum* (pea)	Indoxacarb 150 g/L EC	> 504 g a.s./ha	-

2.9.7. Summary of effects on other terrestrial organisms (flora and fauna)

No data available.

2.9.8. Summary of effects on biological methods for sewage treatment

Test type/organism	end point

Activated sludge	EC50 >1000 mg DPX-MP062/L[1]
Pseudomonas sp	-

[1] Mixture containing approximately 75% DPX-KN128.

2.9.9. Summary of product exposure and risk assessment

Summary of product exposure and risk assessment for terrestrial vertebrates

The risk assessment for birds and mammals is carried out following the latest guidance document by EFSA (Anonymous 2009: Guidance Document on risk assessment for Birds & Mammals on request from EFSA. EFSA Journal 2009; 7(12):1438. European Food Safety Authority).

The acute risk to birds of indoxacarb was assessed by calculating toxicity exposure ratios (TER_a).

Screening level acute TER_a for birds exposed to Indoxacarb 150 g/L EC in maize and leafy vegetables

Scenario	Species	LD_{50} (dietary) (mg a.s./kg bw/d)	SV (90^{th} %)[a]	Rate applied (kg a.s./ha)	MAF[b]	DDD[c]	TER[d]	Regulation (EC) 546/2011 trigger
Maize	Small omnivorous bird	73.5	158.8	0.0375	1.1	6.55	11.2	10
Leafy vegetables	Small omnivorous bird	73.5	158.8	0.0375	1.8	10.72	**6.9**	10

The TER_a value for maize is greater than the TER trigger of 10, indicating acceptable risk to birds from Indoxacarb 150 g/L EC, when used in accordance with the proposed label. The TER_a value for leafy vegetables is below the Regulation (EC) 546/2011 trigger of 10, indicating a need for refinement.

Tier 1 TER_a for birds exposed to Indoxacarb 150 g/L EC in leafy vegetables

Scenario	Species	LD_{50} (dietary) (mg a.s./kg bw/d)	SV (90^{th} %)[a]	Rate applied (kg a.s./ha)	MAF[b]	DDD[c]	TER[d]	Regulation (EC) 546/2011 trigger
Leafy vegetables BBCH 10-49	Small granivorous bird "finch"	73.5	27.4	0.0375	1.8	1.9	39.7	10
Leafy vegetables BBCH ≥50	Small granivorous bird "finch"	73.5	8.2	0.0375	1.8	0.6	132.8	10
Leafy vegetables BBCH 10-49	Small omnivorous bird "lark"	73.5	24.0	0.0375	1.8	1.6	45.4	10
Leafy vegetables BBCH ≥50	Small omnivorous bird "lark"	73.5	7.2	0.0375	1.8	0.5	151.2	10
Leafy vegetables BBCH 10-19	Medium herbivorous/granivorous bird "pigeon"	73.5	90.6	0.0375	1.8	6.1	12.0	10
Leafy vegetables BBCH 10-19	Small insectivorous bird "wagtail"	73.5	26.8	0.0375	1.8	1.8	40.6	10
Leafy vegetables BBCH ≥20	Small insectivorous bird "wagtail"	73.5	25.2	0.0375	1.8	1.7	43.2	10

Screening level acute TER_a for birds exposed to IN-JT333 in maize and leafy vegetables

Scenario	Species	LD_{50} (dietary) (mg a.s./kg bw/d)	SV (90^{th} %)[a]	Rate applied (kg a.s./ha)	MAF[b]	DDD[c]	TER[d]	Regulation (EC) 546/2011 trigger
Maize	Small omnivorous bird	1750	158.8	0.0375	1.1	6.55	267.2	10
Leafy vegetables	Small omnivorous bird	1750	158.8	0.0375	1.8	10.72	163.3	10

The TER_a values are greater than the Regulation (EC) 546/2011 trigger of 10, indicating acceptable acute risk to birds from indoxacarb and IN-JT333 following application of Indoxacarb 150 g/L EC at the proposed label rates.

Exposure *via* Drinking Water

Acute drinking water risk assessment

Tier 1 avian acute drinking water TER_a for Indoxacarb 150 g/L EC–Leaf scenario

	LD_{50} (mg a.s./kg bw/day)	**DWR for small granivorous bird (15.3 g bw) in L/kg bw/d**	**PEC_{pool} (mg a.s./L)**	**TER**	**Regulation (EC) 546/2011 Trigger**
Leaf scenario (PEC_{pool})	73.5	0.46	37.5	**4.3**	10

Tier 1 avian acute drinking water TER_a for IN-JT333–Leaf scenario

	LD_{50} (mg/kg bw/day)	**DWR for small granivorous bird (15.3 g bw) in L/kg bw/d**	**PEC_{pool} (mg a.s./L)**	**TER**	**Regulation (EC) 546/2011 Trigger**
Leaf scenario (PEC_{pool})	1750	0.46	37.5	101.4	10

The TER for exposure to birds from the consumption of pooled spray applications of Indoxacarb 150 g/L EC is below the relevant Commission Regulation (EU) 546/2011 criterion of 10.

Possible mitigation measures for the use on lettuce that might be applied at national level:
- apply only at early stages of crop development (before BBCH 19 in the case of lettuce) or
- provide bird netting on the crop after application.

Puddle Scenario:

Drinking water risk assessment - ratio of effective application rate to acute toxicity endpoint for birds potentially exposed to indoxacarb-puddle scenario

Crop	**LD_{50} (mg a.s./kg bw/d)**	**Rate applied (g a.s./ha)**	**MAF_{90}**	**AR_{eff}**	**HQ**	**Trigger value**
Maize	73.5	37.5	1.7	64.0	0.87	3000
Leafy vegetables	73.5	37.5	3.4	126.1	1.72	3000

Drinking water risk assessment - ratio of effective application rate to acute toxicity endpoint for birds potentially exposed to IN-JT333-puddle scenario

Crop	**LD_{50} (mg/kg bw/d)**	**Rate applied (g a.s./ha)**	**MAF_{90}**	**AR_{eff}**	**HQ**	**Trigger value**
Maize	1750	37.5	1.9	70.6	0.04	3000
Leafy vegetables	1750	37.5	3.8	140.6	0.08	3000

The HQ values are lower than the EFSA Journal 2009: 7(12):1438 trigger value, indicating acceptable acute risk to birds from indoxacarb following application of Indoxacarb 150 g/L EC at all proposed label rates.

The long-term risk to birds of indoxacarb was assessed by calculating toxicity exposure ratios (TER_{lt}).

Screening Step TER_{lt} for birds exposed to Indoxacarb 150 g/L EC in maize and leafy vegetables

Scenario	Species	LD_{50}/10 (avian repro) (mg a.s./kg bw/d)	SV (mean)	Rate applied (kg a.s./ha)	MAF	TWA	DDD	TER	Regulation (EC) 546/2011 trigger
Maize	Small omnivorous bird	7.35	64.8	0.0375	1.3	0.53	1.67	**4.4**	5
Leafy vegetables	Small omnivorous bird	7.35	64.8	0.0375	2.2	0.53	2.83	**2.6**	5

The TER_{lt} values are below the Regulation (EC) 546/2011 trigger of 5, indicating a need for refinement.

Tier 1 reproductive TER_{lt} for birds exposed to Indoxacarb 150 g/L EC in maize and leafy vegetables

Scenario	Species	LD_{50}/10 (mg a.s./kg bw/d)	SV (mean)	Rate applied (kg a.s./ha)	MAF	TWA	DDD	TER	Trigger value
Maize BBCH 30-39	Medium granivorous bird "game bird"	7.35	1.5	0.0375	1.3	0.53	0.04	189.6	5
Maize BBCH >40	Medium granivorous bird "game bird"	7.35	0.8	0.0375	1.3	0.53	0.02	355.6	5
Maize BBCH 30-39	Small omnivorous bird “lark”	7.35	5.4	0.0375	1.3	0.53	0.14	52.7	5
Maize BBCH >40	Small omnivorous bird “lark”	7.35	2.7	0.0375	1.3	0.53	0.07	105.4	5
Maize BBCH 30-39	Medium herbivorous/granivorous bird "pigeon"	7.35	11.4	0.0375	1.3	0.53	0.29	25.0	5
Maize BBCH >40	Medium herbivorous/granivorous bird "pigeon"	7.35	5.7	0.0375	1.3	0.53	0.15	49.9	5
Maize BBCH ≥20	Small insectivorous bird “wagtail”	7.35	4.8	0.0375	1.3	0.53	0.12	59.3	5
Leafy vegetables BBCH 10-49	Small granivorous bird "finch"	7.35	12.6	0.0375	2.2	0.53	0.55	13.3	5
Leafy vegetables BBCH >50	Small granivorous bird "finch"	7.35	3.8	0.0375	2.2	0.53	0.17	44.2	5
Leafy vegetables BBCH 10-49	Small omnivorous bird “lark”	7.35	10.9	0.0375	2.2	0.53	0.48	15.4	5
Leafy vegetables BBCH >50	Small omnivorous bird “lark”	7.35	3.3	0.0375	2.2	0.53	0.14	50.9	5
Leafy vegetables Leaf development BBCH 10-19	Medium herbivorous/granivorous bird "pigeon"	7.35	22.7[f]	0.0375	2.2	0.53	1.00	7.3	5
Leafy vegetables BBCH 10-19	Small insectivorous bird “wagtail”	7.35	11.3	0.0375	2.2	0.53	0.49	14.9	5
Leafy vegetables BBCH >20	Small insectivorous bird “wagtail”	7.35	9.7	0.0375	2.2	0.53	0.42	17.3	5

The TER_{lt} exceed the Regulation (EC) 546/2011 trigger of 5 for all maize and leafy vegetables scenarios, indicating safe use of the product.

Reproductive drinking water risk assessment

Drinking water risk assessment-ratio of effective application rate to reproductive toxicity endpoint for birds potentially exposed to indoxacarb-puddle scenario

Crop	LD_{50}/10 (mg a.s./kg bw/d)	Rate applied (g a.s./ha)	MAF_m	AR_{eff}	HQ	Trigger value
Maize	7.35	37.5	1.7	64.0	8.71	3000
Leafy vegetables	7.35	37.5	3.4	126.1	17.16	3000

The HQ_{lt} values are below the trigger value proposed by EFSA:1438 (2009), indicating acceptable chronic risk to birds from indoxacarb (DPX-KN128) following application of Indoxacarb 150 g/L EC at the proposed label rates.

Effects of secondary poisoning

The risk assessment via secondary poisoning for metabolites of indoxacarb was not accepted by RMS due to the low reliability of the proposed values of log Kow and BCF. The risk assessment via secondary poisoning for metabolites of indoxacarb is therefore not finalized.

Tier 1 food-chain from earthworms to earthworm-eating birds risk assessment for Indoxacarb 150 g/L EC

Substance	Crop	PEC plateau soil mg/kg	BCF dry soil	DDD dry soil mg/kg/d	TER dry soil	TER Trigger
Indoxacarb	Maize	0.042	5.24	0.23	31.8	5
	Leafy vegetables	0.169	5.24	0.93	7.9	5

Tier 1 food-chain from fish to fish-eating birds risk assessment for Indoxacarb 150 g/L EC and metabolites

Substance	Crop	PEC water mg/L	Fish BCF L/kg	PEC fish mg/kg	DDD mg/kg/d	TER	TER Trigger
Indoxacarb	Maize	0.00014	77.3	0.01	0.00	8059	5
	Leafy vegetables	0.00053	77.3	0.04	0.00	2128	5

The acute risk to wild mammals was assessed by calculation of toxicity exposure ratios (TER_a).

Screening step TER_a for mammals exposed to Indoxacarb 150 g/L EC in maize and leafy vegetables

Scenario	Species	LD_{50} (acute) (mg a.s./kg bw/d)	SV (90^{th} %)	Rate applied (kg a.s./ha)	MAF	DDD	TER	Trigger value
Maize	Small herbivorous mammal	146.4	136.4	0.0375	1.1	5.63	26.0	10
Leafy vegetables	Small herbivorous mammal	146.4	136.4	0.0375	1.8	9.21	15.9	10

Screening step TER_a for mammals exposed to IN-JT333 in maize and leafy vegetables

Scenario	Species	LD_{50} (acute) (mg/kg bw/d)	SV (90^{th} %)	Rate applied (kg a.s./ha)	MAF	DDD	TER	Trigger value
Maize	Small herbivorous mammal	39	136.4	0.0375	1.1	5.63	**6.9**	10
Leafy vegetables	Small herbivorous mammal	39	136.4	0.0375	1.8	9.21	**4.2**	10

The TER_a values are above the trigger value of 10, indicating acceptable risk to mammals from indoxacarb when used in accordance with the proposed label for Indoxacarb 150 g/L EC. The metabolite IN-JT333 TER_a values are below the trigger of 10, indicating a need for refinement.

Tier 1 TER_a for mammals exposed to IN-JT333 in maize and leafy vegetables

Scenario	Species	LD_{50} (acute) (mg/kg bw/d)	SV (90^{th} %)	Rate applied (kg a.s./ha)	MAF	DDD	TER	Trigger value
Maize BBCH ≥20	Small insectivorous mammal "shrew"	39	5.4	0.0375	1.15	0.22	175.1	10
Maize BBCH 30-39	Small herbivorous mammal "vole"	39	68.2	0.0375	1.15	2.81	13.9	10
Maize BBCH >40	Small herbivorous mammal "vole"	39	34.1	0.0375	1.15	1.41	27.7	10
Maize BBCH 30-39	Small omnivorous mammal "mouse"	39	8.6	0.0375	1.15	0.35	109.9	10
Maize BBCH >40	Small omnivorous mammal "mouse"	39	4.3	0.0375	1.15	0.18	219.9	10
Leafy vegetables BBCH 10-19	Small insectivorous mammal "shrew"	39	7.6	0.0375	1.77	0.51	76.0	10
Leafy vegetables BBCH >20	Small insectivorous mammal "shrew"	39	5.4	0.0375	1.77	0.36	107.0	10
Leafy vegetables BBCH 40-49	Small herbivorous mammal "vole"	39	136.4	0.0375	1.77	9.29	**4.2**	10
Leafy vegetables BBCH >50	mall herbivorous mammal "vole"	39	40.9	0.0375	1.77	2.77	14.1	10
Leafy vegetables BBCH 13-59	Large herbivorous mammal "Lagomorph"	39	35.1	0.0375	1.77	2.36	16.5	10
Leafy vegetables BBCH 10-49	Small omnivorous mammal "mouse"	39	17.2	0.0375	1.77	1.16	33.6	10
Leafy vegetables BBCH >50	Small omnivorous mammal "mouse"	39	5.2	0.0375	1.77	0.35	111.1	10

The TER_a for IN-JT333 is below the relevant Commission Regulation (EU) 546/2011 trigger of 10 for voles foraging in leafy vegetables. This suggests that the metabolite IN-JT333 may pose a risk to small herbivorous mammals and therefore a refined risk assessment was conducted.

Refined risk assessment for IN-JT333 – leafy vegetables

Refined acute TER_a for small herbivorous mammals and dietary exposure to IN-JT333 from applications of Indoxacarb 150 g/L EC

Crop/focal Species	BBCH growth stage	Rate Applied (kg a.s./ha)	Short Cut Value	MAF	$DDD_{refined}$ (mg/kg bw/d)	LD_{50} (mg/kg bw/d)	TER	Trigger value
Leafy vegetable - Small herbivorous mammal "vole"	40-49	0.0375	136.4	1.8	0.93	39	42.0	10

The TER_a values for all proposed uses of Indoxacarb 150 g/L EC are greater than the Commission Regulation (EU) 546/2011 trigger of 10, indicating that Indoxacarb 150 g/L EC will not pose an acute risk to wild mammals

Acute drinking water risk assessment – puddle scenario

Drinking water risk assessment - ratio of effective application rate to acute toxicity endpoint for mammals potentially exposed to Indoxacarb 150 g/L EC

Crop	LD_{50} (mg a.s./kg bw/d)	Rate applied (g a.s./ha)	MAF_{90}	AR_{eff}	HQ	Trigger value
Maize	146.4	37.5	1.7	64.0	0.43	3000
Leafy vegetables	146.4	37.5	3.4	126.1	0.86	3000

Drinking water risk assessment - ratio of effective application rate to acute toxicity endpoint for mammals potentially exposed to IN-JT333

Crop	LD_{50} (mg a.s./kg bw/d)	Rate applied (g a.s./ha)	MAF_{90}	AR_{eff}	HQ	Trigger value
Maize	39	37.5	1.9	70.6	1.81	3000
Leafy vegetables	39	37.5	3.8	140.6	3.60	3000

The HQ values are lower than the EFSA Journal 2009: 7(12):1438 trigger value, indicating acceptable acute risk to mammals from indoxacarb (DPX-KN128) following application of Indoxacarb 150 g/L EC at the proposed label rates.

Long-term toxicity exposure ratio (TER_{lt}) for mammals

Screening step TER_{lt} for mammals exposed to Indoxacarb 150 g/L EC in maize and leafy vegetables

Scenario	Species	NOEL mammal repro. (mg a.s./kg bw/d)	RUD_{SV} (mean)	Rate applied (kg a.s./ha)	MAF	DDD	TER	Trigger Value
Maize	Small herbivorous mammal	0.6	72.3	0.0375	1.25	1.87	**0.32**	5
Leafy vegetables	Small herbivorous mammal	0.6	72.3	0.0375	2.23	3.16	**0.19**	5

The TER_{lt} values are below the Regulation (EC) 546/2011 trigger of 5, indicating a need for a Tier 1 risk assessment.

The NOAEL retained by RMS to be used in the refined risk assessment is of 0.68 mg DPX-KN128/kg bw/d.

Tier 1 TER_{lt} for mammals exposed to Indoxacarb 150 g/L EC in maize and leafy vegetables

Scenario	Species	NOAEL mammal repro. (mg a.s./kg bw/d)	RUD_{SV} (mean)	Rate applied (kg a.s./ha)	MAF	DDD	TER	Regulation (EC) 546/2011 trigger
Maize BBCH ≥20	Small insectivorous mammal "shrew"	0.68	1.9	0.0375	1.3	0.05	13.9	5
Maize BBCH 30-39	Small herbivorous mammal "vole"	0.68	36.1	0.0375	1.3	0.94	**0.7**	5
Maize BBCH ≥40	Small herbivorous mammal "vole"	0.68	18.1	0.0375	1.3	0.47	**1.5**	5
Maize BBCH 30-39	Small omnivorous mammal "mouse"	0.68	3.9	0.0375	1.3	0.10	6.7	5
Maize BBCH ≥40	Small omnivorous mammal "mouse"	0.68	1.9	0.0375	1.3	0.05	13.9	5
Leafy vegetables BBCH 10-19	Small insectivorous mammal "shrew"	0.68	4.2	0.0375	2.2	0.19	**3.7**	5
Leafy vegetables BBCH ≥20	Small insectivorous mammal "shrew"	0.68	1.9	0.0375	2.2	0.08	8.2	5
Leafy vegetables BBCH 40-49	Small herbivorous mammal "vole"	0.68	72.3	0.0375	2.2	3.1	**0.2**	5
Leafy vegetables BBCH ≥50	Small herbivorous mammal "vole"	0.68	21.7	0.0375	2.2	0.96	**0.7**	5
Leafy vegetables all seasons	Large herbivorous mammal "Lagomorph"	0.68	14.3	0.0375	2.2	0.63	**1.1**	5
Leafy vegetables BBCH 10-49	Small omnivorous mammal "mouse"	0.68	7.8	0.0375	2.2	0.35	**2.0**	5
Leafy vegetables BBCH ≥50	Small omnivorous mammal "mouse"	0.68	2.3	0.0375	2.2	0.10	6.8	5

For use on maize: The TERlt values for Indoxacarb 150 g/L EC are higher than the Commission Regulation (EU) 546/2011 trigger value of 5 for all wild mammal indicator species with the exception of voles in maize. For voles, TER_{lt} values are below the trigger value of 5. A refined long-term risk assessment is therefore triggered for voles in maize.

No refinement was proposed by the applicant for this use as the endpoint proposed by the applicant for the TER calculations (4.6 mg/kg bw/d) led to acceptable risks at Tier 1 for all indicator species. As this refined was not accepted by RMS, the long-term risk assessment for small herbivorous mammals is not finalized.

For use on lettuce: The TERlt values for Indoxacarb 150 g/L EC are higher than the Commission Regulation (EU) 546/2011 trigger value of 5 for only two indicator species and at later growth stages (BBCH ≥50 for small omnivorous and BBCH ≥20 for small insectivorous). The TER_{lt} values for small and large herbivorous (at all intended growth stages), for small omnivorous (at early growth stage) and small insectivorous mammal (at early growth stage) are below the trigger value of 5.

No refinement was proposed by the applicant for large herbivorous, small omnivorous and small insectivorous mammals for this use as the endpoint proposed by the applicant for the TER calculations (4.6 mg/kg bw/d) led to acceptable risks at Tier 1 for these indicator species. As this refined was not accepted by RMS, the long-term risk assessment for large herbivorous, small omnivorous and small insectivorous mammals is not finalized.

For voles, TER_{lt} values are also below the trigger value of 5. A refined long-term risk assessment is therefore triggered for voles in maize. The risk refinement proposed by the applicant is based on several parameters (refined toxicity endpoint, PD values, relevance of the vole). None of these options were accepted by RMS due to the lack of justification. Therefore the long-term risk assessment for small herbivorous mammals is not finalized.

Reproductive drinking water risk assessment

Drinking water risk assessment - ratio of effective application rate to reproductive toxicity endpoint for mammals potentially exposed to Indoxacarb 150 g/L EC - puddle scenario

Crop	NOAEL (mg a.s./kg bw/d)	Rate applied (g a.s./ha)	MAF_m	AR_{eff}	HQ	Trigger value
Maize	0.68	37.5	1.7	64.0	94.1	3000
Leafy vegetables	0.68	37.5	3.4	126.1	185.4	3000

The HQ_{lt} values are below the trigger value proposed by EFSA Journal 2009: 7(12):1438, indicating acceptable chronic risk to mammals from indoxacarb (DPX-KN128) following application of Indoxacarb 150 g/L EC at all proposed label rates.

Effects of secondary poisoning

The risk assessment via secondary poisoning for metabolites of indoxacarb was not accepted by RMS due to the low reliability of the proposed values of log Kow and BCF. The risk assessment via secondary poisoning for metabolites of indoxacarb is therefore not finalized.

Exposure from earthworm to earthworm-eating mammals

Tier 1 food-chain from earthworms to earthworm-eating mammals risk assessment for Indoxacarb 150 g/L EC

Substance	Crop	PEC soil mg/kg	BCF dry soil	DDD dry soil mg/kg/d	TER dry soil	TER Trigger
Indoxacarb	Maize	0.042	5.24	0.28	**2.41**	5
	Leafy vegetables	0.169	5.24	1.13	**0.60**	5

The TER are below the trigger of 5. The risk for earthworms eating-mammals needs to be refined. In the absence of further data, the risk assessment for effects via secondary poisoning is considered not finalized.

Tier 1 food-chain from fish to fish-eating mammal risk assessment for Indoxacarb 150 g/L EC

Substance	Crop	PEC water mg /L	fish BCF L/kg	PEC fish mg /kg	DDD mg/kg/d	TER	TER Trigger
Indoxacarb	Maize	0.00014	77.3	0.01	0.00	835	5
	Leafy vegetables	0.00053	77.3	0.04	0.00	220	5

The TER calculated for the active substance show acceptable risk for fish-eating mammals.

Summary of product exposure and risk assessment for aquatic organisms

The relevant guidance was the Guidance Document on Aquatic Ecotoxicology[4] and the updated guidance of EFSA (2013)[5].

Use on maize:

$FOCUS_{sw}$ step 1-3 - TERs for indoxacarb – Maize at 37.5 g a.s./ha [2 applications]

Scenario	PEC global max (µg L)	fish acute	fish chronic	Aquatic invertebrates	Aquatic invertebrates-prolonged	Algae	Sed. dweller prolonged
		Oncorhynchus mykiss	*Pimephales promelas*	*Mysidopsis bahia*	*Mysidopsis bahia*	*Pseudokirchneriella subcapitata*	*Chironomus riparius*
		LC_{50}	NOEC	EC_{50}	NOEC	EC_{50}	EC10
		>170 µg/L	67.5 µg/L	>126 µg/L	14.5 µg/L	>79.3 µg/L	1.68 µg/L
FOCUS Step 1	1.941	**87**	34	**64**	**7**	40	**0.87**
FOCUS Step 2							
North Europe	0.345	492		365	42		**4.87**
South Europe	0.546	311		230	26		**3.08**

[4] SANCO/3268/2001 rev. 4 Final (17 October 2002)

[5] EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues), 2013. Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters. EFSA Journal 2013;11(7):3290, 186 pp. doi:10.2903/j.efsa.2013.3290. Available online: www.efsa.europa.eu/efsajournal

FOCUS Step 3						
Single application						
D3, ditch	0.195	871	646	74		**8.62**
D4, pond	0.008	21250	15750	1812		210
D4, stream	0.170	1000	741	85		**9.88**
D5, pond	0.008	21250	15750	1812		210
D5, stream	0.180	944	700	80		**9.33**
D6, ditch	0.193	880	652	75		**8.70**
R1, pond	0.011	15454	11454	1318		152
R1, stream	0.136	1250	926	106		12
R2, stream	0.182	934	692	79		**9.23**
R3, stream	0.192	885	656	75		**8.75**
R4, stream	0.134	1268	940	108		12
Multiple applications						
D3, ditch	0.170	1000	741	85		**9.88**
D4, pond	0.010	17000	12600	1450		168
D4, stream	0.148	1148	851	97		11.35
D5, pond	0.010	17000	12600	1450		168
D5, stream	0.165	1030	763	87		10.18
D6, ditch	0.171	994	736	84		**9.82**
R1, pond	0.014	12142	9000	1035		120
R1, stream	0.117	1452	1076	123		14.36
R2, stream	0.157	1082	802	92		10.70
R3, stream	0.165	1030	763	87		10.18
R4, stream	0.159	1069	792	91		10.57
Trigger		100	10	100	10	10	10

FOCUS$_{sw}$ step 4 - TERs indoxacarb – Maize at 37.5 g a.s./ha [2 applications]

Organisms *Chironomus riparius***:**

Toxicity endpoint: 1.68 µg/L

Mitigation options	[x] m non-spray buffer zone	[x] m vegetated buffer strip	PECsw (µg/L)	TER	Trigger
FOCUS Step 4					
Single application					
D3, ditch	10	10	0.034	49	10
D4, stream	10	10	0.038	44	10
D5, stream	10	10	0.040	42	10
D6, ditch	10	10	0.034	49	10
R2, stream	10	10	0.041	41	10
R3, stream	10	10	0.043	39	10
Multiple applications					
D3, ditch	10	10	0.028	60	10
D6, ditch	10	10	0.028	60	10

Sediment exposure

FOCUS$_{sed}$ step 1-3 - TERs for indoxacarb – Maize at 37.5 g a.s./ha [2 applications]

Scenario	PEC global max (µg/kg sed)	Sed. dweller prolonged
		Chironomus riparius
		NOEC
		2.92 µg/kg sed
FOCUS Step 1	81.782	**0.04**
FOCUS Step 2		
North Europe	14.279	**0.20**
South Europe	27.299	**0.11**
FOCUS Step 3		

Single application

D3, ditch	0.104	28
D4, pond	0.025	116
D4, stream	0.014	208
D5, pond	0.024	121
D5, stream	0.012	243
D6, ditch	0.055	53.
R1, pond	0.042	69
R1, stream	0.315	**9.27**
R2, stream	0.651	**4.49**
R3, stream	0.253	11.54
R4, stream	0.667	**4.38**
Multiple applications		
D3, ditch	0.100	29
D4, pond	0.033	88
D4, stream	0.015	194
D5, pond	0.029	100
D5, stream	0.043	67
D6, ditch	0.141	20
R1, pond	0.083	35
R1, stream	0.316	**9.24**
R2, stream	0.651	**4.49**
R3, stream	0.715	**4.08**
R4, stream	0.667	**4.38**
Trigger		10

FOCUS$_{sed}$ step 4 - TERs indoxacarb – Maize at 37.5 g a.s./ha [2 applications]

Organisms *Chironomus riparius***:**
Toxicity endpoint: 2.92 µg/kg sed

Mitigation options	**[x] m non-spray buffer zone**	**[x] m vegetated buffer strip**	**PECsed (µg/kg sed)**	**TER**	**Trigger**

FOCUS Step 4					
Single application					
R1, stream	10	10	0.060	48	10
R2, stream	10	10	0.103	28	10
R3, stream	10	10	0.047	62	10
Multiple applications					
R1, stream	10	10	0.060	48	10
R2, stream	10	10	0.103	28	10
R3, stream	10	10	0.127	22	10
R4, stream	10	10	0.147	19	10

TER for metabolites (use on maize)

IN-JT333

FOCUS$_{sw}$ step 1-2 - TERs for IN-JT333 – Maize at 37.5 g a.s./ha [2 applications]

Scenario	PEC global max (µg L)	fish acute	fish chronic	Aquatic invertebrates	Algae
		Oncorhynchus mykiss	*Pimephales promelas*	*Daphnia magna*	*Pseudokirchneriella subcapitata*
		LC_{50}	NOEC	EC_{50}	EC_{50}
		10.5	2.42	>29	>7.5
FOCUS Step 1	0.330	**31**	**7.33**	**87**	22
FOCUS Step 2					
North Europe	0.079	132	30	367	94
South Europe	0.079	132	30	367	94
Trigger		100	10	100	10

Note: IN-KN125 is acutely more toxic for fish than IN-JT333. The toxicity of isomer IN-KN125 was used for the acute TER for fish as this isomer represents the major form of metabolite IN-JT333 (mixture of IN-KN125 and IN-KN124).

FOCUS$_{sed}$ step 1-3 - TERs for IN-JT333 – Maize at 37.5 g a.s./ha [2 applications]

Scenario	PEC global max (µg /kg sed)	Sed. dweller prolonged
		Chironomus riparius
		NOEC

		96 µg/kg sed
FOCUS Step 1	30.535	**3.14**
FOCUS Step 2		
North Europe	2.633	36
South Europe	4.428	21
Trigger		10

IN-JU873

FOCUS$_{sw}$ step 1-2 - TERs for IN-JU873 – Maize at 37.5 g a.s./ha [2 applications]

Scenario	**PEC global max (µg L)**	**fish acute**	**Aquatic invertebrates**	**Algae**
		Oncorhynchus mykiss	*Daphnia magna*	*Pseudokirchneriella subcapitata*
		LC_{50}	EC_{50}	EC_{50}
		441	379	>265
FOCUS Step 1	0.151	2920	2509	1754
FOCUS Step 2				
North Europe	0.011	40090	34454	24090
South Europe	0.023	19173	16478	11521
Trigger		100	100	10

IN-KG433

FOCUS$_{sw}$ step 1-2 - TERs for IN-KG433 – Maize at 37.5 g a.s./ha [2 applications]

Scenario	**PEC global max (µg L)**	**fish acute**	**Aquatic invertebrates**	**Algae**
		Oncorhynchus mykiss	*Mysidopsis bahia*	*Pseudokirchneriella subcapitata*
		LC_{50}	EC_{50}	EC_{50}
		>220	1.45*	7.92*
FOCUS	6.889	**31**	**0.21**	**1.15**

Step 1				
FOCUS Step 2				
North Europe	0.219	1004	**6.62**	36
South Europe	0.402	547	**3.61**	19
Trigger		100	100	10

* As no reliable value is available for aquatic invertebrates and algae, the toxicity of the parent compound divided by 10 was used for TER calculations.

Note: The test item IN-KG433 was not found (<LOD) at 0 and 48 hours in the study Dupont-36478 (acute toxicity on *Mysidopsis bahia)*. This study cannot be considered reliable and a new study is required. Applicant indicated that a new study has been scheduled.

Based on FOCUS PEC at Step 2, the TER values remain below the trigger. No PECsw values are available at Step 3. The acute risk for aquatic invertebrates is not finalized.

FOCUS$_{sed}$ step 1-2 - TERs for IN-KG433 – Maize at 37.5 g a.s./ha [2 applications]

Scenario	**PEC global max (µg /kg sed)**	**Sed. dweller prolonged**
		Chironomus riparius
		NOEC
		170 µg/kg sed
FOCUS Step 1	21.568	**7.88**
FOCUS Step 2		
North Europe	0.675	251
South Europe	1.250	136
Trigger		10

IN-KT413

FOCUS$_{sw}$ step 1-2 - TERs for IN-KT413 – Maize at 37.5 g a.s./ha [2 applications]

Scenario	PEC global max (µg L)	fish acute	Aquatic invertebrates	Aquatic invertebrates prolonged	Algae	Sed. dweller prolonged
		Oncorhynchus mykiss	*Daphnia magna*	*Daphnia magna*	*Pseudokirchneriella subcapitata*	*Chironomus riparius*
		LC_{50}	EC_{50}	NOEC	EC_{50}	NOEC
		>1060	967	3900	105000	24
FOCUS Step 1	3.679	288	262	1060	28540	**6.52**
FOCUS Step 2						
North Europe	0.396	2676	2441	9848	265151	60
South Europe	0.396	2676	2441	9848	265151	60
Trigger		100	100	10	10	10

$FOCUS_{sed}$ step 1-2 - TERs for IN-KT413 – Maize at 37.5 g a.s./ha [2 applications]

Scenario	PEC global max (µg /kg sed)	Sed. dweller prolonged
		Chironomus riparius
		NOEC
		7500 µg/kg sed
FOCUS Step 1	11.707	640
FOCUS Step 2		
North Europe	1.006	7455
South Europe	1.107	6775
Trigger		10

IN-MK638

$FOCUS_{sw}$ step 1-2 - TERs for IN-MK638 – Maize at 37.5 g a.s./ha [2 applications]

Scenario	PEC global max (µg L)	fish acute	Aquatic invertebrates	Algae
		Oncorhynchus mykiss	*Mysidopsis bahia*	*Pseudokirchneriella subcapitata*
		LC_{50}	EC_{50}	EC_{50}
		28000	41100	37200
FOCUS Step 1	2.463	11368	16686	15103
FOCUS Step 2				
North Europe	0.166	168674	247590	224096
South Europe	0.272	102941	151102	136764
Trigger		100	100	10

IN-MK643

$FOCUS_{sw}$ step 1-2 - TERs for IN-MK643 – Maize at 37.5 g a.s./ha [2 applications]

Scenario	PEC global max (µg L)	fish acute	Aquatic invertebrates	Algae
		Oncorhynchus mykiss	*Mysidopsis bahia*	*Pseudokirchneriella subcapitata*
		LC_{50}	EC_{50}	EC_{50}
		6990	16400	59700
FOCUS Step 1	0.912	7664	17982	65460
FOCUS Step 2				
North Europe	0.086	81279	190697	694186
South Europe	0.173	40404	94797	345086
Trigger		100	100	10

IN-KB687

$FOCUS_{sw}$ step 1-2 - TERs for IN-KB687 – Maize at 37.5 g a.s./ha [2 applications]

Scenario	PEC global max (µg L)	fish acute	Aquatic invertebrates	Algae
		Oncorhynchus mykiss	*Mysidopsis bahia*	*Pseudokirchneriella subcapitata*
		LC_{50}	EC_{50}	EC_{50}
		11900	7200	>2260
FOCUS Step 1	1.950	6102	3692	1158
FOCUS Step 2				
North Europe	0.071	167605	101408	31830
South Europe	0.071	167605	101408	31830
Trigger		100	100	10

IN-MP819

$FOCUS_{sw}$ step 1-2 - TERs for IN-MP819 – Maize at 37.5 g a.s./ha [2 applications]

Scenario	PEC global max (µg L)	fish acute	Aquatic invertebrates	Algae
		Oncorhynchus mykiss	*Daphnia magna*	*Pseudokirchneriella subcapitata*
		LC_{50}	EC_{50}	EC_{50}
		>368	60	>358
FOCUS Step 1	0.178	2067	337	2011
FOCUS Step 2				
North Europe	0.083	4433	722	4313
South Europe	0.083	4433	722	4313
Trigger		100	100	10

$FOCUS_{sed}$ step 1-2 - TERs for IN-MP819 – Maize at 37.5 g a.s./ha [2 applications]

Scenario	PEC global max (µg /kg sed)	Sed. dweller prolonged
		Chironomus riparius
		NOEC
		86200 µg/kg sed
FOCUS Step 1	3.764	22901
FOCUS Step 2		
North Europe	1.024	84179
South Europe	1.024	84179
Trigger		10

IN-MS775

FOCUS$_{sw}$ step 1-2 - TERs for IN-MS775 – Maize at 37.5 g a.s./ha [2 applications]

Scenario	PEC global max (µg L)	fish acute	Aquatic invertebrates	Algae
		Oncorhynchus mykiss	*Daphnia magna*	*Pseudokirchneriella subcapitata*
		LC_{50}	EC_{50}	EC_{50}
		>3.96	>5.67	>52
FOCUS Step 1	0.079	**50**	**71**	658
FOCUS Step 2				
North Europe	0.040	>99	141	1300
South Europe	0.040	>99	141	1300
Trigger		100	100	10

The TER_a for IN-MS775 is slightly below the trigger value. However, the respective 96-hour LC_{50} value is a greater than value, which can be attributed to the solubility limit of the metabolite in the

study, indicating a higher actual value. Therefore, RMS assumes a sufficient margin of safety for this metabolite.

FOCUS$_{sed}$ step 1-2 - TERs for IN-MS775 – Maize at 37.5 g a.s./ha [2 applications]

Scenario	PEC global max (µg /kg sed)	Sed. dweller prolonged
		Chironomus riparius
		NOEC
		2200 µg/kg sed
FOCUS Step 1	0.571	3852
FOCUS Step 2		
North Europe	0.49	4489
South Europe	0.49	4489
Trigger		10

IN-U8E24

FOCUS$_{sw}$ step 1-2 - TERs for IN-U8E24 – Maize at 37.5 g a.s./ha [2 applications]

Scenario	PEC global max (µg L)	fish acute	Aquatic invertebrates	Algae
		Oncorhynchus mykiss	*Daphnia magna*	*Pseudokirchneriella subcapitata*
		LC_{50}	EC_{50}	EC_{50}
		46500	>12000	55200
FOCUS Step 1	13113	3384	15567	13113
FOCUS Step 2				
North Europe	72998	18838	86656	72998
South Europe	40754	10517	48379	40754
Trigger		100	100	10

IN-UYG24

FOCUS$_{sw}$ step 1-2 - TERs for IN-UYG24 – Maize at 37.5 g a.s./ha [2 applications]

Scenario	PEC global max (µg L)	fish acute	Aquatic invertebrates	Algae
		Oncorhynchus mykiss	*Daphnia magna*	*Pseudokirchneriella subcapitata*
		LC_{50}	EC_{50}	EC_{50}
		>115000	>120000	>106000
FOCUS Step 1	0.131	877863	916031	809160
FOCUS Step 2				
North Europe	0.107	1074766	1121495	990654
South Europe	0.107	1074766	1121495	990654
Trigger		100	100	10

IN-ML438

FOCUS$_{sw}$ step 1-2 - TERs for IN-ML438 – Maize at 37.5 g a.s./ha [2 applications]

Scenario	PEC global max (µg L)	fish acute	Aquatic invertebrates	Algae
		Oncorhynchus mykiss	*Mysidopsis bahia*	*Pseudokirchneriella subcapitata*
		LC_{50}	EC_{50}	EC_{50}
		>17*	>12.6*	>7.93*
FOCUS Step 1	0.082	207	154	97
FOCUS Step 2				
North Europe	0.009	1889	1400	881
South Europe	0.012	1417	1050	661
Trigger		100	100	10

*No toxicity data is available for this metabolite. The toxicity of the active substance divided by 10 was used as surrogate.

RMS conclusions on the use on maize:

Considering the toxicity of the active substance on sediment dwelling organisms, a 10 m buffer zone and 10 m Vegetated Filter Strip were considered necessary for the use on maize.

No reliable data on IN-KG433 for acute toxicity on *Mysidopsis bahia* are available. A new study is required. Applicant indicated that a new study has been scheduled. Based on FOCUS PEC at Step 2, the TER values, based on the toxicity of the active substance divided by 10, remain below the trigger. No PECsw values are available at Step 3. The acute risk for aquatic invertebrates is therefore not finalized for IN-KG433.

For all other metabolites, TER calculations are available for the surface water compartment and show acceptable risks without mitigation measures. As no toxicity data is available for IN-ML438, the toxicity of the active substance divided by 10 was used as surrogate.

TER calculations are also available for the sediment compartment for five metabolites: IN-JT333, IN-KG433, IN-KT413, IN-MP819 and IN-MS775. Acceptable risk via sediment was demonstrated for all five metabolites without mitigation measures.

No TER calculation in sediment is available for IN-JU873, IN-ML438, IN-MK643, IN-MK638, IN-KB687, IN-U8E24, IN-UYG24, IN-MH304 and IN-MF014. Toxicity data on other aquatic organisms are available for IN-JU873, IN-MK643, IN-MK638, IN-KB687, IN-U8E24, IN-UYG24. These metabolites are clearly of low toxicity to other aquatic groups. No TER was considered necessary.

No toxicity data are available for IN-ML438, IN-MH304 and IN-MF014. According to the PECsed available for Step 2, IN-ML438, IN-MH304 and IN-MF014 are expected at low concentrations in the sediment and the risk via sediment is considered covered by the risk assessment conducted for the active substance.

Use on lettuce:

FOCUS$_{sw}$ step 1-3 - TERs for indoxacarb – Lettuce at 37.5 g a.s./ha [4 applications]

Scenario	PEC global max (µg L)	fish acute	fish chronic	Aquatic invertebrates	Aquatic invertebrates-prolonged	Algae	Sed. dweller prolonged
		Oncorhynchus mykiss	*Pimephales promelas*	*Mysidopsis bahia*	*Mysidopsis bahia*	*Pseudokirchneriella subcapitata*	*Chironomus riparius*
		LC_{50}	NOEC	EC_{50}	NOEC	EC_{50}	EC10
		>170 µg/L	67.5 µg/L	>126 µg/L	14.5 µg/L	>79.3 µg/L	1.68 µg/L
FOCUS Step 1	7.763	**21**	**8.70**	**16.23**	**1.87**	10.22	**0.22**
FOCUS Step 2							

North Europe	1.547	109	43	**81**	**9.37**	**1.09**
South Europe	1.547	109	43	**81**	**9.37**	**1.09**
FOCUS Step 3						
Single application						

D3, ditch (1st)	0.237	531	61	**7.09**
D3, ditch (2nd)	0.237	531	61	**7.09**
D4, pond (1st)	0.008	15750	1812	210
D4, stream (1st)	0.189	666	76	**8.89**
D6, ditch (1st)	0.232	543	62	**7.24**
R1, pond (1st)	0.013	9692	1115	129
R1, pond (2nd)	0.017	7411	852	98
R1, stream (1st)	0.156	807	92	10.77
R1, stream (2nd)	0.157	802	92	10.70
R2, stream (1st)	0.206	611	70	**8.16**
R2, stream (2nd)	0.21	600	69	**8.00**
R3, stream (1st)	0.219	575	66	**7.67**
R3, stream (2nd)	0.22	572	65	**7.64**
R4, stream (1st)	0.156	807	92	10.77
R4, stream (2nd)	0.155	812	93	10.84
Multiple applications				
D3, ditch (1st)	0.160	787	90	10.50
D3, ditch (2nd)	0.160	787	90	10.50
D4, pond (1st)	0.008	15750	1812	210
D4, stream (1st)	0.127	992	114	13.23
D6, ditch (1st)	0.159	792	91	10.57
R1, pond (1st)	0.062	2032	233	27
R1, pond (2nd)	0.032	3937	453	52
R1, stream (1st)	0.165	763	87	10.18
R1, stream (2nd)	0.207	608	70	**8.12**
R2, stream (1st)	0.139	906	104	12.09
R2, stream (2nd)	0.141	893	102	11.91
R3, stream (1st)	0.149	845	97	11.28
R3, stream (2nd)	0.265	475	54	**6.34**

R4, stream (1st)	0.370			340	39		**4.54**
R4, stream (2nd)	0.250			504	58		**6.72**
Trigger		100	10	100	10	10	10

FOCUS$_{sw}$ step 4 - TERs indoxacarb – Lettuce at 37.5 g a.s./ha [4 applications]

Organisms *Chironomus riparius***:**
Toxicity endpoint: 1.68 µg/L

Mitigation options	**[x] m non-spray buffer zone**	**[x] m vegetated buffer strip**	**PECsw (µg/L)**	**TER**	**Trigger**
FOCUS Step 4*					
Single application					
D3, ditch (1st)	10	10	Not available	-	10
D3, ditch (2nd)	10	10	Not available	-	10
D4, stream (1st)	10	10	Not available	-	10
D6, ditch (1st)	10	10	Not available	-	10
R2, stream (1st)	10	10	0.040	42	10
R2, stream (2nd)	10	10	0.041	40	10
R3, stream (1st)	10	10	0.088	19	10
R3, stream (2nd)	10	10	0.071	23	10
Multiple applications					
R1, stream (2nd)	10	10	0.080	21	10
R3, stream (2nd)	10	10	0.077	21	10
R4, stream (1st)	10	10	0.175	**9.60**	10
R4, stream (2nd)	10	10	0.127	13.23	10
Single application	20	20			
D3, ditch (1st)	20	20	0.018	93	10
D3, ditch (2nd)	20	20	0.018	93	10
D4, stream (1st)	20	20	0.019	88	10
D6, ditch (1st)	20	20	0.017	98	10
Multiple applications					
R4, stream (1st)	20	20	0.092	18	10

Sediment exposure

FOCUS$_{sed}$ step 1-3 - TERs for indoxacarb – Lettuce at 37.5 g a.s./ha [4 applications]

Scenario	PEC global max (µg /kg sediment)	Sed. dweller prolonged
		Chironomus riparius
		NOEC
		2.92 µg/kg sed
FOCUS Step 1	327.128	**0.01**
FOCUS Step 2		
North Europe	78.497	**0.04**
South Europe	78.497	**0.04**
FOCUS Step 3		
Single application		
D3, ditch (1st)	0.160	18
D3, ditch (2nd)	0.160	18
D4, pond (1st)	0.014	208
D4, stream (1st)	0.127	22
D6, ditch (1st)	0.159	18
R1, pond (1st)	0.057	51
R1, pond (2nd)	0.084	34
R1, stream (1st)	0.215	13
R1, stream (2nd)	0.177	16
R2, stream (1st)	0.139	21
R2, stream (2nd)	0.141	20
R3, stream (1st)	0.277	10.54
R3, stream (2nd)	0.169	17
R4, stream (1st)	0.385	**7.58**
R4, stream (2nd)	0.280	10.43
Multiple applications		
D3, ditch (1st)	0.139	21
D3, ditch (2nd)	0.130	22

D4, pond (1st)	0.050	58
D4, stream (1st)	0.007	417
D6, ditch (1st)	0.069	42
R1, pond (1st)	0.218	13
R1, pond (2nd)	0.551	**5.30**
R1, stream (1st)	3.168	**0.92**
R1, stream (2nd)	2.164	**1.35**
R2, stream (1st)	2.640	**1.11**
R2, stream (2nd)	2.572	**1.14**
R3, stream (1st)	1.217	**2.40**
R3, stream (2nd)	0.984	**2.97**
R4, stream (1st)	0.975	**2.99**
R4, stream (2nd)	0.453	**6.45**
Trigger		10

FOCUS$_{sed}$ step 4 - TERs indoxacarb – Lettuce at 37.5 g a.s./ha [4 applications]

Organisms *Chironomus riparius***:**

Toxicity endpoint: 2.92 µg/kg sed

Mitigation options	[x] m non-spray buffer zone	[x] m vegetated buffer strip	PECsed (µg/kg sed)	TER	Trigger
FOCUS Step 4*					
Single application					
R4, stream (1st)	10	10	0.124	23	10
Multiple applications					
R1, pond (2nd)	10	10	0.229	12	10
R1, stream (1st)	10	10	0.501	**5.83**	10
R1, stream (2nd)	10	10	0.369	**7.91**	10
R2, stream (1st)	10	10	0.428	**6.82**	10
R2, stream (2nd)	10	10	0.399	**7.32**	10
R3, stream (1st)	10	10	0.202	14	10
R3, stream (2nd)	10	10	0.177	16	10
R4, stream (1st)	10	10	0.263	11.10	10
R4, stream (2nd)	10	10	0.117	24	10
Multiple applications					
R1, stream (1st)	20	20	0.175	16	10
R1, stream (2nd)	20	20	0.136	21	10
R2, stream (1st)	20	20	0.152	19	10
R2, stream (2nd)	20	20	0.137	21	10

TER for metabolites (use on lettuce)

IN-JT333

FOCUS$_{sw}$ step 1-3 - TERs for IN-JT333 – Lettuce at 37.5 g a.s./ha [4 applications]

Scenario	PEC global max (µg L)	fish acute	fish chronic	Aquatic invertebrates	Algae
		Oncorhynchus mykiss	*Pimephales promelas*	*Daphnia magna*	*Pseudokirchneriella subcapitata*
		LC_{50}	NOEC	EC_{50}	EC_{50}
		10.5	2.42	>29	>7.5
FOCUS Step 1	0.660	**15**	**3.67**	**43.94**	11.36
FOCUS Step 2					
North Europe	0.079	132	30	367	94
South Europe	0.079	132	30	367	94
Trigger		100	10	100	10

Note: IN-KN125 is acutely more toxic for fish than IN-JT333. The toxicity of isomer IN-KN125 was used for the acute TER for fish as this isomer represents the major form of metabolite IN-JT333 (mixture of IN-KN125 and IN-KN124).

FOCUS$_{sed}$ step 1-3 - TERs for IN-JT333 – Lettuce at 37.5 g a.s./ha [4 applications]

Scenario	PEC global max (µg /kg sed)	Sed. dweller prolonged
		Chironomus riparius
		NOEC
		96 µg/kg sed
FOCUS Step 1	61.069	**1.57**
FOCUS Step 2		
North Europe	11.481	**8.36**
South Europe	11.481	**8.36**
FOCUS Step 3		
Single application		
D3, ditch (1st)	0.412	233
D3, ditch (2nd)	0.412	233
D4, pond (1st)	0.050	1920
D4, stream (1st)	0.000	96000
D6, ditch (1st)	0.412	233
R1, pond (1st)	0.050	1920
R1, pond (2nd)	0.050	1920
R1, stream (1st)	0.124	774
R1, stream (2nd)	0.143	671
R2, stream (1st)	0.050	1920
R2, stream (2nd)	0.540	177
R3, stream (1st)	0.075	1280
R3, stream (2nd)	0.054	1777
R4, stream (1st)	0.030	3200
R4, stream (2nd)	0.022	4363
Multiple applications		
D3, ditch (1st)	1.112	86

D3, ditch (2nd)	1.112	86
D4, pond (1st)	0.125	768
D4, stream (1st)	0.000	96000
D6, ditch (1st)	1.112	86
R1, pond (1st)	0.125	768
R1, pond (2nd)	0.125	768
R1, stream (1st)	0.695	138
R1, stream (2nd)	0.511	187
R2, stream (1st)	0.182	527
R2, stream (2nd)	1.523	63
R3, stream (1st)	0.448	214
R3, stream (2nd)	0.216	444
R4, stream (1st)	0.158	607
R4, stream (2nd)	0.080	1200
Trigger		10

IN-JU873

FOCUS$_{sw}$ step 1-2 - TERs for IN-JU873 – Lettuce at 37.5 g a.s./ha [4 applications]

Scenario	**PEC global max (µg L)**	**fish acute**	**Aquatic invertebrates**	**Algae**
		Oncorhynchus mykiss	*Daphnia magna*	*Pseudokirchneriella subcapitata*
		LC_{50}	EC_{50}	EC_{50}
		441	379	>265
FOCUS Step 1	0.302	1460	1254	877
FOCUS Step 2				
North Europe	0.067	6582	5656	3955
South Europe	0.067	6582	5656	3955
Trigger		100	100	10

IN-KG433

FOCUS$_{sw}$ step 1-2 - TERs for IN-KG433 – Lettuce at 37.5 g a.s./ha [4 applications]

Scenario	PEC global max (µg L)	fish acute	Aquatic invertebrates	Algae
		Oncorhynchus mykiss	*Mysidopsis bahia*	*Pseudokirchneriella subcapitata*
		LC_{50}	EC_{50}	EC_{50}
		>220	1.45*	7.92*
FOCUS Step 1	13.778	**15**	**0.11**	**0.57**
FOCUS Step 2				
North Europe	0.820	268	**1.77**	**9.66**
South Europe	0.820	268	**1.77**	**9.66**
Trigger		100	100	10

* As no reliable value is available for aquatic invertebrates and algae, the toxicity of the parent compound divided by 10 was used for TER calculations.

Note: The test item IN-KG433 was not found (<LOD) at 0 and 48 hours in the study Dupont-36478 (acute toxicity on *Mysidopsis bahia)*. This study cannot be considered reliable and a new study is required. Applicant indicated that a new study has been scheduled.

Based on FOCUS PEC at Step 2, the TER values remain below the trigger for aquatic invertebrates and algae. No PECsw values are available at Step 3. The acute risk for aquatic invertebrates and algae is therefore not finalized.

FOCUS$_{sed}$ step 1-2 - TERs for IN-KG433 – Lettuce at 37.5 g a.s./ha [4 applications]

Scenario	PEC global max (µg /kg sed)	Sed. dweller prolonged
		Chironomus riparius
		NOEC
		170 µg/kg sed
FOCUS Step 1	43.136	**3.94**
FOCUS Step 2		

North Europe	2.557	66
South Europe	2.557	66
Trigger		10

IN-KT413

FOCUS$_{sw}$ step 1-2 - TERs for IN-KT413 – Lettuce at 37.5 g a.s./ha [4 applications]

Scenario	PEC global max (µg L)	fish acute	Aquatic invertebrates	Aquatic invertebrates prolonged	Algae	Sed. dweller prolonged
		Oncorhynchus mykiss	*Daphnia magna*	*Daphnia magna*	*Pseudokirchneriella subcapitata*	*Chironomus riparius*
		LC_{50}	EC_{50}	NOEC	EC_{50}	NOEC
		>1060	967	3900	105000	24
FOCUS Step 1	7.359	144	131	529	14268	**3.26**
FOCUS Step 2						
North Europe	0.545	1944	1774	7155	192660	44
South Europe	0.545	1944	1774	7155	192660	44
Trigger		100	100	10	10	10

FOCUS$_{sed}$ step 1-2 - TERs for IN-KT413 – Lettuce at 37.5 g a.s./ha [4 applications]

Scenario	PEC global max (µg /kg sed)	Sed. dweller prolonged
		Chironomus riparius
		NOEC
		7500 µg/kg sed
FOCUS Step 1	23.414	320
FOCUS Step 2		
North Europe	1.672	4485

South Europe	1.672	4485
Trigger		10

IN-MK638

FOCUS$_{sw}$ step 1-2 - TERs for IN-MK638 – Lettuce at 37.5 g a.s./ha [4 applications]

Scenario	PEC global max (µg L)	fish acute	Aquatic invertebrates	Algae
		Oncorhynchus mykiss	*Mysidopsis bahia*	*Pseudokirchneriella subcapitata*
		LC_{50}	EC_{50}	EC_{50}
		28000	41100	37200
FOCUS Step 1	4.927	5682	8341	7550
FOCUS Step 2				
North Europe	0.764	36649	53795	48691
South Europe	0.645	43410	63720	57674
Trigger		100	100	10

IN-MK643

FOCUS$_{sw}$ step 1-2 - TERs for IN-MK643 – Lettuce at 37.5 g a.s./ha [4 applications]

Scenario	PEC global max (µg L)	fish acute	Aquatic invertebrates	Algae
		Oncorhynchus mykiss	*Mysidopsis bahia*	*Pseudokirchneriella subcapitata*
		LC_{50}	EC_{50}	EC_{50}
		6990	16400	59700
FOCUS Step 1	1.825	3830	8986	32712
FOCUS Step 2				

North Europe	0.516	13546	31782	115697
South Europe	0.516	13546	31782	115697
Trigger		100	100	10

IN-KB687

FOCUS$_{sw}$ step 1-2 - TERs for IN-KB687 – Lettuce at 37.5 g a.s./ha [4 applications]

Scenario	**PEC global max (µg L)**	**fish acute**	**Aquatic invertebrates**	**Algae**
		Oncorhynchus mykiss	*Mysidopsis bahia*	*Pseudokirchneriella subcapitata*
		LC_{50}	EC_{50}	EC_{50}
		11900	7200	>2260
FOCUS Step 1	3.901	3050	1845	579
FOCUS Step 2				
North Europe	0.103	115533	69902	21941
South Europe	0.103	115533	69902	21941
Trigger		100	100	10

IN-MP819

FOCUS$_{sw}$ step 1-2 - TERs for IN-MP819 – Lettuce at 37.5 g a.s./ha [4 applications]

Scenario	**PEC global max (µg L)**	**fish acute**	**Aquatic invertebrates**	**Algae**
		Oncorhynchus mykiss	*Daphnia magna*	*Pseudokirchneriella subcapitata*
		LC_{50}	EC_{50}	EC_{50}
		>368	60	>358
FOCUS Step 1	0.357	1030	168	1002

FOCUS Step 2				
North Europe	0.083	4433	722	4313
South Europe	0.083	4433	722	4313
Trigger		100	100	10

FOCUS$_{sed}$ step 1-2 - TERs for IN-MP819 – Lettuce at 37.5 g a.s./ha [4 applications]

Scenario	**PEC global max (µg /kg sed)**	**Sed. dweller prolonged**
		Chironomus riparius
		NOEC
		86200 µg/kg sed
FOCUS Step 1	7.528	11450
FOCUS Step 2		
North Europe	1.564	55115
South Europe	1.564	55115
Trigger		10

IN-MS775

FOCUS$_{sw}$ step 1-2 - TERs for IN-MS775 – Lettuce at 37.5 g a.s./ha [4 applications]

Scenario	**PEC global max (µg L)**	**fish acute**	**Aquatic invertebrates**	**Algae**
		Oncorhynchus mykiss	*Daphnia magna*	*Pseudokirchneriella subcapitata*
		LC_{50}	EC_{50}	EC_{50}
		>3.96	>5.67	>52
FOCUS Step 1	0.158	**25**	**35**	329
FOCUS Step 2				

North Europe	0.040	>99	141	1300
South Europe	0.040	>99	141	1300
Trigger		100	100	10

The TER_a for IN-MS775 is slightly below the trigger value based on FOCUS Step 2 PEC values. However, the respective 96-hour LC_{50} value is a greater than value, which can be attributed to the solubility limit of the metabolite in the study, indicating a higher actual value. Therefore, RMS assumes a sufficient margin of safety for this metabolite.

$FOCUS_{sed}$ step 1-2 - TERs for IN-MS775 – Lettuce at 37.5 g a.s./ha [4 applications]

Scenario	**PEC global max (µg /kg sed)**	**Sed. dweller prolonged**
		Chironomus riparius
		NOEC
		2200 µg/kg sed
FOCUS Step 1	1.142	1926
FOCUS Step 2		
North Europe	0.749	2937
South Europe	0.749	2937
Trigger		10

IN-U8E24

$FOCUS_{sw}$ step 1-2 - TERs for IN-U8E24 – Lettuce at 37.5 g a.s./ha [4 applications]

Scenario	**PEC global max (µg L)**	**fish acute**	**Aquatic invertebrates**	**Algae**
		Oncorhynchus mykiss	*Daphnia magna*	*Pseudokirchneriella subcapitata*
		LC_{50}	EC_{50}	EC_{50}

		46500	>12000	55200
FOCUS Step 1	7.09	6559	1693	7786
FOCUS Step 2				
North Europe	2.723	17077	4407	20272
South Europe	2.219	20955	5408	24876
Trigger		100	100	10

IN-UYG24

FOCUS$_{sw}$ step 1-2 - TERs for IN-UYG24 – Lettuce at 37.5 g a.s./ha [4 applications]

Scenario	**PEC global max (µg L)**	**fish acute**	**Aquatic invertebrates**	**Algae**
		Oncorhynchus mykiss	*Daphnia magna*	*Pseudokirchneriella subcapitata*
		LC_{50}	EC_{50}	EC_{50}
		>115000	>120000	>106000
FOCUS Step 1	0.262	438931	458015	404580
FOCUS Step 2				
North Europe	0.16	718750	750000	662500
South Europe	0.16	718750	750000	662500
Trigger		100	100	10

IN-ML438

FOCUS$_{sw}$ step 1-2 - TERs for IN-ML438 – Lettuce at 37.5 g a.s./ha [4 applications]

Scenario	**PEC global max (µg L)**	**fish acute**	**Aquatic invertebrates**	**Algae**
		Oncorhynchus mykiss	*Mysidopsis bahia*	*Pseudokirchneriella subcapitata*

		LC_{50}	EC_{50}	EC_{50}
		>17*	>12.6*	>7.93*
FOCUS Step 1	0.164	104	77	48
FOCUS Step 2				
North Europe	0.035	486	360	227
South Europe	0.035	486	360	227
Trigger		100	100	10

*No toxicity data is available for this metabolite. The toxicity of the active substance divided by 10 was used as surrogate.

RMS conclusions on the use on lettuce:

Considering the toxicity of the active substance on sediment dwelling organisms, a 20 m buffer zone and 20 m Vegetated Filter Strip were considered necessary for the use on lettuce.

No reliable data on IN-KG433 for acute toxicity on *Mysidopsis bahia* are available. A new study is required. Applicant indicated that a new study has been scheduled. Based on FOCUS PEC at Step 2, the TER values, based on the toxicity of the active substance divided by 10, remain below the trigger. No PECsw values are available at Step 3. The acute risk for aquatic invertebrates is therefore not finalized for IN-KG433.

For all other metabolites, TER calculations are available for the surface water compartment and show acceptable risks without mitigation measures. As no toxicity data are available for IN-ML438, the toxicity of the active substance divided by 10 was used as surrogate.

TER calculations are also available for the sediment compartment for five metabolites: IN-JT333, IN-KG433, IN-KT413, IN-MP819 and IN-MS775. Acceptable risk via sediment was demonstrated for all five metabolites without mitigation measures.

No TER calculation in sediment is available for IN-JU873, IN-ML438, IN-MK643, IN-MK638, IN-KB687, IN-U8E24, IN-UYG24, IN-MH304 and IN-MF014. Toxicity data on other aquatic organisms are available for IN-JU873, IN-MK643, IN-MK638, IN-KB687, IN-U8E24, IN-UYG24. These metabolites are clearly of low toxicity to other aquatic groups. No TER was considered necessary.

No toxicity data are available for IN-ML438, IN-MH304 and IN-MF014. According to the PECsed available for Step 2, IN-ML438, IN-MH304 and IN-MF014 are expected at low concentrations in the sediment and the risk via sediment is considered covered by the risk assessment conducted for the active substance.

Summary of product exposure and risk assessment for bees

The risk assessment used here follows the EC Guidance Document on Terrestrial Ecotoxicology (SANCO/10329, 17 October 2002).

Acute oral exposure Q_{HO}

Acute oral toxicity to honey bees (*Apis mellifera*)

Exposure route	Test compound	Application rate (g a.s./ha)	LD_{50} (µg a.s./bee)	Hazard quotient (Q_{HO})
Acute oral	Indoxacarb	37.5	0.232	**161**
Acute oral	Indoxacarb 150 g/L EC	37.5	0.11	**341**

Acute contact toxicity to honey bees (*Apis mellifera*)

Exposure route	Test compound	Application rate (g a.s./ha)	LD_{50} (µg a.s./bee)	Hazard quotient (Q_{HC})
Acute contact	Indoxacarb	37.5	0.0682	**550**
Acute contact	Indoxacarb 150 g/L EC	37.5	0.08	**469**

The acute oral and contact hazard quotients are exceeding the Regulation (EC) 546/2011 trigger value of 50. Therefore, further work, including semi-field and tunnel studies, was conducted with Indoxacarb 150 g/L EC to assess the potential risk to bees and bumblebees under actual conditions of use. The results of these tests are summarized above.

The risk of Indoxacarb 150 g/L EC to honey bees under actual use conditions will depend on the level of exposure. Exposure of honey bees to residues of Indoxacarb 150 g/L EC will depend on the presence of flowers during the times in which applications of Indoxacarb 150 g/L EC are made (crop growth stage) and the attractiveness of these flowers as a source of nectar or pollen. The risk to honey bees from applications of Indoxacarb 150 g/L EC to lettuce is considered to be negligible, because timing of applications in lettuce is before crop flowering (BBCH 13-59 for seed crops).

The effects observed in semi-field tunnel studies (11) with honey bees and *Phacelia tanacetifolia* or oil seed rape suggest that a potential short-term (mortality, decrease of foraging, behaviour) and long-term risk to honey bees from applications of Indoxacarb 150 g/L EC may occur in flowering crops that are highly attractive to honey bees. These effects, and particularly effects on development (observed in brood feeding tests and OECD75 testings), are expected even for an application in the evening after bee-flight. Several studies showed brood/compensation indices lower than in control, and termination rates higher than in the control. RMS considers that it is treatment related. The studies available with the less attractive crop maize are either not considered fully reliable (tunnel study) or not representative of an application during the flowering period (field study). It is then recommended to avoid application during flowering for these crops too. Strong effects of Indoxacarb 150 g/L EC were observed when applied on wheat treated with sugar solution (during and after bee flight). It is then also recommended to avoid application during honeydew production periods.

Summary of product exposure and risk assessment for non-target arthropods other than bees

Tier 1 summary of non-target arthropod in-field and off-field hazard quotients (HQ) for Indoxacarb 150 g/L EC use

Species	LR_{50} (g a.s./ha)	In-field HQ	Off-field HQ	Trigger
Leafy vegetables, 4 × 37.5 g a.s./ha				
T. pyri	220.5	0.46	0.01	2
A. rhopalosiphi	5.1	**19.9**	0.37	2
Maize, 2 × 37.5 g a.s./ha				
T. pyri	220.5	0.29	0.01	2
A. rhopalosiphi	5.1	**12.5**	0.30	2

In-field and off-field hazard quotients for *Typhlodromus pyri* are below the ESCORT II trigger value of 2 and therefore indicate that the risk to this standard sensitive non-target arthropod species is acceptable for all intended uses of Indoxacarb 150 g/L EC.

In-field hazard quotients for *Aphidius rhopalosiphi* are above the ESCORT II trigger value of 2 for all uses of Indoxacarb 150 g/L EC and therefore trigger a higher-tiered assessment and the evaluation of potential effects on additional species.

Off-field hazard quotients for *Aphidius rhopalosiphi* are below the ESCORT II trigger value of 2 for all proposed uses of Indoxacarb 150 g/L EC, therefore indicating that the off-field risk to this standard sensitive non-target arthropod species is acceptable for all intended uses of Indoxacarb 150 g/L EC.

Based on the results of the higher-tier studies with *Aphidius rhopalosiphi*, *Chrysoperla carnea,* and *Orius laevigatus* using a worst-case exposure scenario that exceeds all proposed uses described in the GAP (4 × 100 g a.s./ha was actually investigated in these studies) transient in-field effects may be expected for *Aphidius rhopalosiphi* and *Chrysoperla carnea,* but not for *Orius laevigatus*. However, when residues of Indoxacarb 150 g/L EC were aged under natural conditions, the effects on both mortality and reproduction for these non-target arthropods were reduced. Aging residues for 28 days after the fourth application resulted in 8.8% mortality and no adverse effect on both fecundity and hatching of *Chrysoperla carnea* when compared to controls. Aging residues for 28 days resulted in 13.2% mortality and 57.8% reduction in reproduction of *Aphidius rhopalosiphi.* A 56-day aging period resulted in 2.5% mortality and 37.6% reduction in reproduction. The results demonstrate clearly that effects decline with time and any in-field effects observed are likely to be short-lived. This ensures that sensitive in-field non-target arthropod populations may recover rapidly for the intended uses with maximum use rates that are much lower than those tested in these studies.

Summary of product exposure and risk assessment for non-target soil meso- and macrofauna

The risk of Indoxacarb 150 g/L EC is assessed according to the Guidance Document on Terrestrial Ecotoxicology (SANCO/10329/2002, October 2002).

Maize at 37.5 g a.s./ha [2 applications]

Test organism	Test substance	Time scale	Soil PEC	TER	Trigger
Eisenia fetida	DPX-KN128	Chronic	0.042 (plateau)	570	5
Eisenia fetida	Indoxacarb 150 g/L EC	Chronic	0.042 (plateau)	255	5

Test organism	Test substance	Time scale	Soil PEC	TER	Trigger
Eisenia fetida	IN-JT333	Chronic	0.007 (plateau)	7837	5
Eisenia fetida	IN-JT333	Chronic	0.007 (plateau)	178	5
Eisenia fetida	IN-JU873	Chronic	0.004 (plateau)	12500	5
Eisenia fetida	IN-KG433	Chronic	0.015 (initial)	3333	5
Eisenia fetida	IN-KT413	Chronic	0.007 (initial)	14285	5
Eisenia fetida	IN-MK638	Chronic	0.004 (initial)	12500	5
Eisenia fetida	IN-MK643	Chronic	0.002 (plateau)	11125	5
Eisenia fetida	IN-KB687	Chronic	0.004 (initial)	12500	5
Eisenia fetida	IN-ML438	Chronic	0.003 (plateau)	798	5
Eisenia fetida	IN-U8E24	Chronic	0.022 (plateau)	109	5
Folsomia candida	DPX-KN128	Chronic	0.042 (plateau)	2542	5
Folsomia candida	Indoxacarb 150 g/L EC	Chronic	0.042 (plateau)	23.8	5
Folsomia candida	IN-JT333	Chronic	0.007 (plateau)	7142	5
Folsomia candida	IN-JU873	Chronic	0.004 (plateau)	25000	5
Folsomia candida	IN-KG433	Chronic	0.015 (initial)	416	5
Folsomia candida	IN-KT413	Chronic	0.007 (initial)	14285	5
Folsomia candida	IN-MK638	Chronic	0.004 (initial)	2537	5
Folsomia candida	IN-MK643	Chronic	0.002 (plateau)	2500	5
Folsomia candida	IN-KB687	Chronic	0.004 (initial)	1562	5
Folsomia candida	IN-ML438	Chronic	0.003 (plateau)	3560	5
Folsomia candida	IN-U8E24	Chronic	0.022 (plateau)	485	5

Test organism	Test substance	Time scale	Soil PEC	TER	Trigger
Hypoaspis aculeifer	DPX-KN128	Chronic	0.042 (plateau)	23809	5
Hypoaspis aculeifer	Indoxacarb 150 g/L EC	Chronic	0.042 (plateau)	340	5
Hypoaspis aculeifer	IN-JT333	Chronic	0.007 (plateau)	14285	5
Hypoaspis aculeifer	IN-JU873	Chronic	0.004 (plateau)	25000	5
Hypoaspis aculeifer	IN-KG433	Chronic	0.015 (initial)	6666	5
Hypoaspis aculeifer	IN-KT413	Chronic	0.007 (initial)	8957	5
Hypoaspis aculeifer	IN-MK638	Chronic	0.004 (initial)	25000	5
Hypoaspis aculeifer	IN-MK643	Chronic	0.002 (plateau)	50000	5
Hypoaspis aculeifer	IN-KB687	Chronic	0.004 (initial)	781	5
Hypoaspis aculeifer	IN-ML438	Chronic	0.003 (plateau)	33333	5
Hypoaspis aculeifer	IN-U8E24	Chronic	0.022 (plateau)	4545	5

Lettuce at 37.5 g a.s./ha [4 applications]

Test organism	Test substance	Time scale	Soil PEC	TER	Trigger
Eisenia fetida	DPX-KN128	Chronic	0.169 (plateau)	142	5
Eisenia fetida	Indoxacarb 150 g/L EC	Chronic	0.169 (plateau)	63	5
Eisenia fetida	IN-JT333	Chronic	0.026 (plateau)	2110	5
Eisenia fetida	IN-JT333	Chronic	0.026 (plateau)	48	5
Eisenia fetida	IN-JU873	Chronic	0.017 (plateau)	2941	5
Eisenia fetida	IN-KG433	Chronic	0.059 (initial)	847	5
Eisenia fetida	IN-KT413	Chronic	0.027 (initial)	3703	5
Eisenia fetida	IN-MK638	Chronic	0.018 (initial)	2777	5

Test organism	Test substance	Time scale	Soil PEC	TER	Trigger
Eisenia fetida	IN-MK643	Chronic	0.009 (plateau)	2472	5
Eisenia fetida	IN-KB687	Chronic	0.015 (initial)	3333	5
Eisenia fetida	IN-ML438	Chronic	0.011 (plateau)	217	5
Eisenia fetida	IN-U8E24	Chronic	0.035 (plateau)	109	5
Folsomia candida	DPX-KN128	Chronic	0.169 (plateau)	632	5
Folsomia candida	Indoxacarb 150 g/L EC	Chronic	0.169 (plateau)	5.9	5
Folsomia candida	IN-JT333	Chronic	0.026 (plateau)	1923	5
Folsomia candida	IN-JU873	Chronic	0.017 (plateau)	5882	5
Folsomia candida	IN-KG433	Chronic	0.059 (initial)	106	5
Folsomia candida	IN-KT413	Chronic	0.027 (initial)	3703	5
Folsomia candida	IN-MK638	Chronic	0.018 (initial)	564	5
Folsomia candida	IN-MK643	Chronic	0.009 (plateau)	555	5
Folsomia candida	IN-KB687	Chronic	0.015 (initial)	416	5
Folsomia candida	IN-ML438	Chronic	0.011 (plateau)	971	5
Folsomia candida	IN-U8E24	Chronic	0.035 (plateau)	305	5
Hypoaspis aculeifer	DPX-KN128	Chronic	0.169 (plateau)	5917	5
Hypoaspis aculeifer	Indoxacarb 150 g/L EC	Chronic	0.169 (plateau)	84	5
Hypoaspis aculeifer	IN-JT333	Chronic	0.026 (plateau)	3846	5
Hypoaspis aculeifer	IN-JU873	Chronic	0.017 (plateau)	5882	5
Hypoaspis aculeifer	IN-KG433	Chronic	0.059 (initial)	1694	5
Hypoaspis aculeifer	IN-KT413	Chronic	0.027 (initial)	2322	5

Test organism	Test substance	Time scale	Soil PEC	TER	Trigger
Hypoaspis aculeifer	IN-MK638	Chronic	0.018 (initial)	5555	5
Hypoaspis aculeifer	IN-MK643	Chronic	0.009 (plateau)	11111	5
Hypoaspis aculeifer	IN-KB687	Chronic	0.015 (initial)	208	5
Hypoaspis aculeifer	IN-ML438	Chronic	0.011 (plateau)	9091	5
Hypoaspis aculeifer	IN-U8E24	Chronic	0.035 (plateau)	2857	5

All long-term TER values are above the Commission Regulation (EU) 546/2011 trigger value of 5, indicating that no unacceptable effects are expected for non-target soil meso- and macrofauna other than earthworms when Indoxacarb 150 g/L EC is applied according to the proposed use pattern.

Summary of product exposure and risk assessment for soil micro-organisms

Risk assessment for effects on nitrogen transformation of non-target micro-organisms

Test item	Endpoint	PEC soil (mg/kg soil)	Risk acceptable?
Indoxacarb 150 g/L EC	<25% effect at day 28 at 8.35 mg formulated product/kg soil dry weight (1.25 mg DPX-KN128/kg soil)	0.169	yes
IN-JT333	<25% effect at day 28 at 60 g/ha (0.08 mg IN-JT333/kg soil dry weight).	0.026	yes
IN-JU873	<25% effect at day 28 at 0.087 and 0.87 mg IN-JU873/kg soil dry weight	0.017	yes
IN-KG433	<25% effect at day 28 at 0.076 mg IN-KG433/kg soil dry weight (14.87%) based on nitrogen levels 28% effect at day 28 at 0.076 mg IN-KG433/kg soil dry weight based on nitrogen transformation	0.059	yes
IN-KT413	<25% effect at day 28 at 0.102 and 1.02 mg IN-KT413/kg soil dry weight	0.027	yes
IN-MK638	<25% effect at day 28 at 0.042 and 0.42 mg IN-MK638/kg soil dry weight	0.018	yes
IN-MK643	<25% effect at day 28 at 0.041 and 0.41 mg IN-MK643/kg soil dry weight	0.009	yes
IN-KB687	<25% effect at day 28 at up to 1.33 mg IN-KB687/kg soil dry weight	0.015	yes
IN-ML438	0.125 mg DPX-KN128/kg soil [a]	0.011	yes
IN-U8E24	0.125 mg DPX-KN128/kg soil [a]	0.035	yes

[a] As a worst-case assumption the endpoint of the parent compound divided by 10 was used.

For metabolite IN-KG433, nitrogen transformation was slightly higher than 25 % (28%) at day 28. It is RMS opinion to consider the risk acceptable for this metabolite as the concentration tested (0.076 mg/kg soil) was above the maximum expected concentration of 0.059 mg/kg soil for the use on lettuce and because the comparison based on nitrogen levels results in effects < 25%. For metabolites IN-ML438 and IN-U8E24, no study was conducted. Considering the endpoint of the parent compound divided by 10 as a worst-case assumption, the risk is acceptable for these metabolites.

Therefore, it is concluded that Indoxacarb 150 g/L EC and its metabolites pose acceptable risk to soil non-target micro-organisms for all proposed uses of Indoxacarb 150 g/L EC.

Summary of product exposure and risk assessment for non-target terrestrial plants

The risk assessment is based on the "Guidance Document on Terrestrial Ecotoxicology", (SANCO/10329/2002 rev2 final, 2002). It is restricted to off-field situations, as non-target plants are non-crop plants located outside the treated area.

Indoxacarb 150 g/L EC: TERs for terrestrial non-target plants based on an application to maize and lettuce (vegetative vigour at 21 days)

Crop	Application rate (g a.s./ha)	Drift value (%)	PEC_{drift} (off-field drift rate in g a.s./ha)	Endpoint used in risk assessment	TER
Maize	37.5	2.77	1.04	ER_{50} >504 g a.s./ha	>485
Lettuce	37.5	2.77	1.04		>485

Indoxacarb 150 g/L EC will not pose an off-field risk to non-target terrestrial plants as the EC_{50} (vegetative vigour) (>504 g a.s./ha) exceeds all uses proposed. It may be concluded that Indoxacarb 150 g/L EC poses no unacceptable risk to plants in the off-crop areas for all uses proposed in the GAP.

2.10. CLASSIFICATION AND LABELLING

Proposed classification according to Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	Not classified		Not classified	Conclusive, but not sufficient for classification*
2.2.	Flammable gases	Not classified		Not classified	Conclusive, but not sufficient for classification*
2.3.	Flammable aerosols	Not classified		Not classified	Conclusive, but not sufficient for classification*
2.4.	Oxidising gases	Not classified		Not classified	Conclusive, but not sufficient for classification*
2.5.	Gases under pressure	Not classified		Not classified	Conclusive, but not sufficient for classification*
2.6.	Flammable liquids	Not classified		Not classified	Conclusive, but not sufficient for classification*
2.7.	Flammable solids	Not classified		Not classified	Conclusive, but not sufficient for classification*
2.8.	Self-reactive substances and mixtures	Not classified		Not classified	Conclusive, but not sufficient for classification*
2.9.	Pyrophoric liquids	Not classified		Not classified	Conclusive, but not sufficient for classification*
2.10.	Pyrophoric solids	Not classified		Not classified	Conclusive, but not sufficient for classification*
2.11.	Self-heating substances and mixtures	Not classified		Not classified	Conclusive, but not sufficient for classification*
2.12.	Substances and mixtures which in contact with water emit flammable gases	Not classified		Not classified	Conclusive, but not sufficient for classification
2.13.	Oxidising liquids	Not classified		Not classified	Conclusive, but not sufficient for classification*
2.14.	Oxidising solids	Not classified		Not classified	Conclusive, but not sufficient for classification*
2.15.	Organic peroxides	Not classified		Not classified	Conclusive, but not sufficient for classification*

2.16.	Substance and mixtures corrosive to metals	Not classified		Not classified	Conclusive, but not sufficient for classification*
3.1.	Acute toxicity - oral	Acute Tox 3 H301		Acute Tox 3 H301	
	Acute toxicity - dermal				Conclusive but not sufficient for classification
	Acute toxicity - inhalation	Acute Tox 4 H332		Acute Tox 4 H332	
3.2.	Skin corrosion / irritation				Conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation				Conclusive but not sufficient for classification
3.4.	Respiratory sensitisation				Data lacking
3.4.	Skin sensitisation	Skin Sens 1B H317		Skin Sens 1B H317	
3.5.	Germ cell mutagenicity				Conclusive but not sufficient for classification
3.6.	Carcinogenicity				Conclusive but not sufficient for classification
3.7.	Reproductive toxicity				Conclusive but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure				Conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure	STOT RE1 H372		STOT RE1 H372	
3.10.	Aspiration hazard				
4.1.	Hazardous to the aquatic environment	Aquatic acute 1; H400 Aquatic chronic 1; H410	Harmonized classification: Acute M factor: 1 Chronic M factor: 1 RMS proposal: Acute M factor: 1 Chronic M factor: 10		
5.1.	Hazardous to the ozone layer				

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification
[3)] Tests should be performed according to CLP criteria (manual UN RTDG)

Labelling: Signal word: Danger
Hazard statements:
H301 – Toxic if swallowed

H332 – Harmful if inhaled
H317 – May cause an allergic skin reaction
H372 – Causes damage to organs (blood, nervous system, heart) through prolonged or repeated exposure
H410: Very toxic to aquatic life with long lasting effects

Proposed notes assigned to an entry:
Notes in accordance with CLP Regulation, Annex VI, Section 1.1.3

Justification:

Human health effects:
A harmonised classification and labelling for indoxacarb was adopted by the ECHA Committee for Risk Assessment (RAC) in June 2011. The resulting classification is available in Commission Regulation (EU) No 944/2013 (5th adaptation to technical and scientific progress of Regulation (EC) No 1272/2008) and the adopted classification for human health is the same as reported above. This classification was considered relevant for indoxacarb DPX-KN128 (99:1) (CAS: 173584-44-6) and for the enantiomeric reaction mass 75:25 S:R (CAS: 144171-61-9).
The toxicological studies available in the CLH report are the same as those evaluated in the first DAR of indoxacarb. Therefore, the majority of studies performed on DPX-KN128 (99:1) and submitted for the purpose of this renewal were not included in the CLH report and were not assessed by the ECHA RAC. Nevertheless, the RMS considers that the newly submitted studies do not change the classification adopted by ECHA RAC.

- Germ cell mutagenicity:
DPX-KN128 (99:1) did not induce mutations in bacteria or mammalian cells *in vitro*, and did not induce structural chromosomal aberrations or polyploidy in mammalian cells *in vitro* either in the presence or in the absence of metabolic activation. DPX-KN128 (99:1) did not induce an increase in micronucleated polychromatic erythrocytes in bone marrow of mice. The same results are reported for the 75:25 S:R enantiomeric blend DPX-MP062. DPX-MP062 (75:25) also did not cause unscheduled DNA synthesis in primary rat hepatocytes *in vitro*.
As a conclusion, the available data indicate that DPX-KN128 (99:1) and DPX-MP062 (75:25) did not show a genotoxic potential and a classification is therefore not considered needed.

- Carcinogenicity:
DPX-JW062 (50:50) did not elicit an oncogenic response in rats or mice at any dose level tested. DPX-KN128 (99:1) has not been tested for carcinogenicity; nevertheless, the comparison of the toxicological data profiles of the two compounds suggest that the results of toxicity studies conducted on the racemic mixture can be used as a surrogate for the pure S enantiomer. Given also that DPX-KN128 (99:1) did not show genotoxic potential, a classification for carcinogenicity is not considered appropriate.

- Reproductive toxicity:
- Adverse effects on sexual function and fertility:

DPX-JW062 (50:50) did not show effects on fertility in a 2-generation rat toxicity study. DPX-KN128 (99:1) has not been tested for effects on reproductive toxicity; nevertheless, the comparison of the toxicological data profiles of the two compounds suggest that the results of toxicity studies conducted on the racemic mixture can be used as a surrogate for the pure S enantiomer. Given also that no effects were reported on reproductive organs in sub-chronic toxicity studies conducted with DPX-KN128 (99:1), a classification for effects on reproduction or fertility is not considered appropriate.

- Adverse effects on development of the offspring:

No severe developmental effects were observed after exposure of pregnant rats to DPX-JW062 (50:50), DPX-MP062 (75:25) and DPX-KN128 (99:1) or after exposure to pregnant rabbits to DPX-JW062 (50:50). Consequently, no classification for effects on development is considered appropriate for DPX-KN128 (99:1).

- Specific Target Organ Toxicity after Repeated Exposure STOT-RE:
A classification as STOT-RE Category 1 is considered appropriate for DPX-KN128 (99:1) on the basis of the following findings and taking into account the dose levels at which they occurred:

- Mortality observed in female rats in the 90-day toxicity study with DPX-MP062 (75:25), supported by mortality data observed in the 28-day rat and mouse studies with DPX-JW062 (50:50);
- Haemolytic anemia observed in all tested species in all studies where the corresponding parameters were assessed;
- Neurotoxicity reported in mice and rats;
- Myocardial necrosis observed in the long-term mouse study.

2.11. RELEVANCE OF METABOLITES IN GROUNDWATER

2.11.1. STEP 1: Exclusion of degradation products of no concern

Indoxacarb metabolites cannot be considered as degradation products of no concern.

2.11.2. STEP 2: Quantification of potential groundwater contamination

Detailed assessment of the potential for Indoxacarb metabolites to reach groundwater is provided in section Volume_3CP_INDOXACARB 150 EC_B-8 for the representative formulation.

Predicted environmental concentrations in groundwater (PEC_{gw}) were calculated for applicable scenarios using the leaching models FOCUS-PEARL 4.4.4 and FOCUS-PELMO 5.5.3.

For every metabolite PECgw were < 0.1 µg/L (max 0.002 µg/L) for all scenarios of the simulated representative uses.

There is no need to further assess relevance for these metabolites.

2.11.3. STEP 3: Hazard assessment – identification of relevant metabolites

2.11.3.1STEP 3, Stage 1: screening for biological activity
Not required

2.11.3.2STEP 3, Stage 2: screening for genotoxicity
Not required

2.11.3.3STEP 3, Stage 3: screening for toxicity
Not required

2.11.4. STEP 4: Exposure assessment – threshold of concern approach

Not required

2.11.5. STEP 5: Refined risk assessment

Not required

2.11.6. Overall conclusion

For every metabolite PECgw were < 0.1 µg/L for all scenarios of the simulated representative uses. There is no need to further assess their relevance.

2.12. CONSIDERATION OF ISOMERIC COMPOSITION IN THE RISK ASSESSMENT

2.12.1. Identity and physical chemical properties

Indoxacarb has been previously enrigestreted as an enriched mixture containg approximately 75 % DPX-KN128 (active) and 25 % IN-KN127 (inactive) with a minimum content of indoxacarb DPX-KN128 (active) of 467 g/kg.
DuPont has implemented further DPX-KN128 process improvements that have led to the consistent production of DPX-KN128 technical without quantifiable level of inactive isomer. Indoxacarb (DPX-KN128) technical material is the basis for this active substance renewal dossier.

2.12.2. Methods of analysis

Analytical method for determinaztion of indoxzaczrb (DPX-KN128) in technical substance was presented. This analytical method cannot separate the two enantiomers (not specific for active S-isomer). However, the assay of the inactive isomer (DPX-KN127) in the technical substance as manufactured using a chiral column was provided and validated for determination of DPX-KN127 with an LOQ of 0.01%.

For analytical methods for risk assessement see Volume 3 B.5.

2.12.3. Mammalian toxicity

Toxicity studies were initially conducted in rats, mice, dogs, and rabbits using DPX-JW062 (50:50 racemic mixture of the DPX-KN128 insecticidally active enantiomer and IN-KN127 the inactive enantiomer). Subsequently, bridging studies were conducted in rats with DPX-MP062 (75:25 isomeric mixture of DPX-KN128 and IN-KN127), and with DPX-KN128 (99% pure) technical active. Acute toxicity and genotoxicity studies were conducted with the isomeric metabolite IN-JT333. Therefore, rats, mice, dogs and/or rabbits were exposed to active and inactive enantiomers of indoxacarb as well as IN-JT333 during toxicity testing.

The results of the sub-chronic toxicity rat studies performed on the three enantiomeric mixtures DPX-JW062 (50:50), DPX-MP062 (75:25) and DPX-KN128 (99:1) showed similar toxicity profile in terms of adverse effects and NOAELs/LOAELs (see Level 2.6). Therefore, the low concentration of the IN-KN127 isomer (<1%) in the DPX-KN128 technical material (>99%) is of low concern.

2.12.4. Operator, Worker, Bystander and Resident exposure

The results of the sub-chronic toxicity rat studies performed on the three enantiomeric mixtures DPX-JW062 (50:50), DPX-MP062 (75:25) and DPX-KN128 (99:1) showed similar toxicity profile in terms of adverse effects and NOAELs/LOAELs (see Level 2.6). Therefore, the potential presence of the IN-KN127 isomer, if any, in the environment is of low concern for the operator, bystander, resident, and worker exposure assessment.

2.12.5. Residues and Consumer risk assessment

Metabolism studies provided for the first inclusion were conducted with the eniantomeric mixture DPX-JW062 (50:50 isomeric mixture of DPX-KN128 and IN-KN127) and showed that there were no enrichment of one enantiomer more than the other.
In animal metabolism studies, also performed with the racemic mixture (50:50), it has been showed that there was some enrichment of DPX-KN128 to IN-KN127 (ratio 2-3:1).
The new active substance based on the pure (>99%) DPX-KN128 technical material will not lead to an interconversion into DPX-KN127.
Moreover, most of residues trials were performed with the DPX-JW062 (50:50), DPX-MP062 (75:25) mixtures but always with the targeted rate expressed as DPX-KN128 which is the insecticidal isomer. Therefore, to obtain a targeted rate with enantiomeric mixtures, a higher dose has to be applied.
As the residue definition takes into account both DPX-KN128 and IN-KN127 isomers, bridging trials performed with the pure DPX-KN128 material led to a lower mean residue level than those performed with the enantiomeric mixtures.

Considering the fact that there were no enantiomeric changes in crops, the low concentrations of residues in crops and livestock and that there are no known mechanisms of converting DPX-KN128 to IN-KN127, the change in enantiomeric ratios may have been due to differences in adsorption and/or distribution of DPX-KN128 versus IN-KN127. Since there would be 1% or less of IN-KN127 in the technical material it is reasonable to assume that any enantiomeric changes would not be significant.

2.12.6. Environmental fate

Environmental fate testing for indoxacarb has been performed using either DPX-JW062 (50:50) or DPX-MP062 (75:25). In several studies, the enantiomeric ratio of the test substance was monitored over time.

In soil, the data recorded in two soils do not give conclusive evidence of the stability of the active substance isomeric ratio, as being uncertain due to analytical procedure. It is however noticeable that it does not provide clear evidence of a faster degradation of one of the isomers. RMS notes that new field trials were provided for the purpose of renewal, and were conducted with active S-isomer IN-KN128. No normalised DT_{50} were derived from these trials. While DT_{50} under ambient conditions are in the same range of laboratory $DegT_{50}$, the normalized values could give opportunity to check whether DT_{50} from field conducted with active isomer only are also comparable to the DT_{50} of the mixtures.

In the aqueous photolysis study, the enantiomeric ratio of DPX-KN128 and IN-KN127 remained constant over time, showing that the enantiomers degrade at the same rate under photolytic conditions.

In sediment, the ratio was not constant over time, but does not provided clear evidence of a faster degradation of one of the isomer. Data from the water/sediment study conducted with the active isomer only do not show significant differences in the degradation rate in sediment compared to data from the study conducted with the mixture.

2.12.7. Ecotoxciology

While testing for ecotoxicology has previously been conducted with the racemic mixtures DPX-JW062 and DPX-MP062, ecotoxicological testing has been updated for this submission. The data package for indoxacarb has now been conducted with the active enantiomer DPX-KN128, and the risk assessment shall be conducted with this new data. DPX-KN128 is 99% pure, therefore no further investigations are required into preferential degradation of a given isomer over another and the relevant routes of exposure related to ecotoxicology.

New ecotoxicological testing has been conducted with the two enantiomers IN-KN125 and IN-KN124 of metabolite IN-JT333. Studies were provided assessing the toxicity of these two enantiomers on an acute basis to *Daphnia magna*, algae, and rainbow trout.

2.13. RESIDUE DEFINITIONS

2.13.1. Definition of residues for exposure/risk assessment

Food of plant origin: sum of indoxacarb and its R enantiomer

Food of animal origin:

- the sum of indoxacarb and its R enantiomer for risk assessment in ruminants and pigs;
- **the sum of indoxacarb, its R enantiomer and its N-decarboxylated metabolite (IN-JT333), expressed as indoxacarb, for risk assessment in poultry (tentative).**

Soil: Indoxacarb, IN-JT333, IN-KG433, IN-KT413, IN JU873, IN-ML438, IN-MK638, IN-KB687, IN-MK643, and IN-U8E24.

Groundwater: Indoxacarb, IN-JT333, IN-KG433, IN-KT413, IN JU873, IN-ML438, IN-MK638, IN-KB687, IN-MK643, and IN-U8E24.

Surface: Indoxacarb, IN-JT333, IN-KG433, IN-KT413, IN JU873, IN-ML438, IN MK638, IN-KB687, IN-MK643, IN-MP819, IN-MS775, IN U8E24, and IN-UYG24.

Sediment: Indoxacarb, IN-JT333, IN-KG433, IN-KT413, IN-ML438, IN-MP819, and IN-MS775.

Air: Indoxacarb

2.13.2. Definition of residues for monitoring

Food of plant origin: sum of indoxacarb and its R enantiomer

Food of animal origin: the sum of indoxacarb and its R enantiomer for enforcement in all commodities of animal origin

Soil: Indoxacarb.

Groundwater: Indoxacarb.

Surface water: Indoxacarb.

Sediment: Indoxacarb.

Air: Indoxacarb.

Level 3

INDOXACARB

3. PROPOSED DECISION WITH RESPECT TO THE APPLICATION

3.1. BACKGROUND TO THE PROPOSED DECISION

3.1.1. Proposal on acceptability against the decision making criteria – Article 4 and annex II of regulation (EC) No 1107/2009

3.1.1.1. Article 4				
		Yes	No	
i)	It is considered that Article 4 of Regulation (EC) No 1107/2009 is complied with. Specifically the RMS considers that authorisation in at least one Member State is expected to be possible for at least one plant protection product containing the active substance for at least one of the representative uses.	X		RMS considers that Indoxacarb can be renewed and that authorizations of PPP can be granted in at least one member States.
3.1.1.2. Submission of further information				
		Yes	No	
i)	It is considered that a complete dossier has been submitted	X		RMS considers that a complete dossier was submitted. However, please refer to Table 3.1.4
ii)	It is considered that in the absence of a full dossier the active substance may be approved even though certain information is still to be submitted because: (a) the data requirements have been amended or refined after the submission of the dossier; or (b) the information is considered to be confirmatory in nature, as required to increase confidence in the decision.			
3.1.1.3. Restrictions on approval				
		Yes	No	
	It is considered that in line with Article 6 of Regulation (EC) No 1107/2009 approval should be subject to conditions and restrictions.		X	
3.1.1.4. Criteria for the approval of an active substance				
Dossier				
		Yes	No	
	It is considered the dossier contains the information needed to establish, where relevant, Acceptable Daily Intake (ADI), Acceptable Operator Exposure Level (AOEL) and Acute Reference Dose (ARfD).	X		Please refer to Level 2.6
	It is considered that the dossier contains the information necessary to	X		Please refer to Level 2.7

	carry out a risk assessment and for enforcement purposes (relevant for substances for which one or more representative uses includes use on feed or food crops or leads indirectly to residues in food or feed). In particular it is considered that the dossier: (a) permits any residue of concern to be defined; (b) reliably predicts the residues in food and feed, including succeeding crops (c) reliably predicts, where relevant, the corresponding residue level reflecting the effects of processing and/or mixing; (d) permits a maximum residue level to be defined and to be determined by appropriate methods in general use for the commodity and, where appropriate, for products of animal origin where the commodity or parts of it is fed to animals; (e) permits, where relevant, concentration or dilution factors due to processing and/or mixing to be defined.			
	It is considered that the dossier submitted is sufficient to permit, where relevant, an estimate of the fate and distribution of the active substance in the environment, and its impact on non-target species.	X		Please refer to Level 2.8 & 2.9
Efficacy				
		Yes	No	
	It is considered that it has been established for one or more representative uses that the plant protection product, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use is sufficiently effective.	X		The efficacy was not assessed for the renewal process of Indoxacarb. Indoxacarb based products are currently registered on the representative uses in some MS. Indoxacarb based products will be re-assessed following the renewal of indoxacarb.
Relevance of metabolites				
		Yes	No	
	It is considered that the documentation submitted is sufficient to permit the establishment of the toxicological, ecotoxicological or environmental relevance of metabolites.	X		However, the risk assessment cannot be finalised for groundwater and aquatic invertebrate considering the lack of information on metabolites IN-U8E24 and IN-KG433 respectivelly (please refer to Level 2 and Table 3.1.5).
Composition				
		Yes	No	
	It is considered that the specification defines the minimum degree of purity, the identity and maximum content of impurities and, where relevant, of isomers/diastereo-isomers and additives, and the content of impurities of toxicological, ecotoxicological or environmental concern	X		The manufacturing process has been modified in order to have a pure active substance without the enantiomer; RMS considers that, for specifications, only data obtained after the current process improvements can be taken into consideration.

	within acceptable limits.			For the active substance, the inactive isomer and some impurities, the certified values proposed by the notifier are not relied on the values given in the profile of batches. Therefore, RMS has proposed new specifications in agreement with profile of batches and with QC data from the current process. This change of specifications is supported by the fact that the new proposed toxicological reference values are based on studies performed with the pure isomer DPX-KN128.
	It is considered that the specification is in compliance with the relevant Food and Agriculture Organisation specification, where such specification exists.	X		RMS proposed to raise the minimum content of the active substance in technical indoxacarb from 90 to 93% without enantiomeric ratio.
	It is considered for reasons of protection of human or animal health or the environment, stricter specifications than that provided for by the FAO specification should be adopted	X		Not necesary
Methods of analysis				
		Yes	No	
	It is considered that the methods of analysis of the active substance, safener or synergist as manufactured and of determination of impurities of toxicological, ecotoxicological or environmental concern or which are present in quantities greater than 1 g/kg in the active substance, safener or synergist as manufactured, have been validated and shown to be sufficiently specific, correctly calibrated, accurate and precise.	X		Adequate analytical methods are available for the determination of indoxacarb significant and relevant impurities in the technical material. All data are considered adequate.
	It is considered that the methods of residue analysis for the active substance and relevant metabolites in plant, animal and environmental matrices and drinking water, as appropriate, shall have been validated and shown to be sufficiently sensitive with respect to the levels of concern.	X		Analytical methods are available to monitor the respective current residue definition in plant material, food of animal origin, soil, drinking water, surface water and air. However some data gaps were identified in the RAR.
	It is confirmed that the evaluation has been carried out in accordance with the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.	X		Analytical methodology is available for determination of active substance and relevant impurities in formulated product. However some data gaps were identified in the RAR and should be provided at the product stage.
Impact on human health				
Impact on human health - ADI, AOEL, ARfD				
		Yes	No	
	It is confirmed that (where relevant) an ADI, AOEL and ARfD can be established with an appropriate safety margin of at least 100 taking into	X		The ADI is set at 0.005 mg/kg bw per day, based on the rat developmental toxicity study performed with DPX-KN128 (99:1) and by using a safety

	account the type and severity of effects and the vulnerability of specific groups of the population.			factor of 100. This is supported by the results of short- and long-term toxicity studies conducted in rats and dogs (see Level 2.6.11). The AOEL is set at 0.003 mg/kg bw per day, based on the rat developmental toxicity study performed with DPX-KN128 (99:1), by using a safety factor of 100 and corrected by the limited oral absorption of 60%. This is supported by the results of short-term toxicity studies conducted in rats and dogs (see Level 2.6.13). The ARfD is set at 0.005 mg/kg bw, based on the rat developmental toxicity study performed with DPX-KN128 (99:1) and by using a safety factor of 100 (see Level 2.6.12). The AAOEL is set at 0.003 mg/kg bw per day, based on the rat developmental toxicity study performed with DPX-KN128 (99:1), by using a safety factor of 100 and corrected by the limited oral absorption of 60% (see Level 2.6.13).
Impact on human health – proposed genotoxicity classification				
		Yes	No	
	It is considered that, on the basis of assessment of higher tier genotoxicity testing carried out in accordance with the data requirements and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as mutagen category 1A or 1B.**		X	Based on the results of *in vitro* and *in vivo* genotoxicity studies, indoxacarb is considered to be not genotoxic (see Level 2.6.4).
Impact on human health – proposed carcinogenicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the carcinogenicity testing carried out in accordance with the data requirements for the active substances, safener or synergist and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as carcinogen category 1A or 1B.**		X	Indoxacarb did not show carcinogenic effects in a 2-year rat study and in a 18-month mouse study (see Level 2.6.5).
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance,			

	safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			
Impact on human health – proposed reproductive toxicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the reproductive toxicity testing carried out in accordance with the data requirements for the active substances, safeners or synergists and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as toxic for reproduction category 1A or 1B.**		X	Indoxacarb did not show effects on fertility in a 2-generation rat toxicity study. No severe developmental effects were observed after exposure of pregnant rats or rabbits to indoxacarb (see Level 2.6.6).
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			
Impact on human health – proposed endocrine disrupting properties classification				
		Yes	No	
i)	It is considered that **the substance SHOULD BE classified or proposed for classification** in accordance with the provisions of Regulation (EC) No 1272/2008, as **carcinogenic category 2 and toxic for reproduction category 2 and on that basis shall be considered to have endocrine disrupting properties**		X	Indoxacarb is not classified or proposed to be classified as carcinogenic category 2 and toxic for reproduction category 2.
ii)	It is considered that **the substance SHOULD BE classified or proposed for classification** in accordance with the provisions of Regulation (EC) No 1272/2008, as **toxic for reproduction category 2 and** in addition the RMS considers the substance **has toxic effects on the endocrine organs and on that basis shall be considered to have**		X	Indoxacarb is not classified or proposed to be classified as toxic for reproduction category 2. Moreover, indoxacarb did not show effects on endocrine organs (see Level 2.6.8).

	endocrine disrupting properties			
iii)	Linked to either i) or ii) immediately above. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			
Fate and behaviour in the environment				
Persistent organic pollutant (POP)				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a persistent organic pollutant (POP) as laid out in Regulation 1107/2009 Annex II Section 3.7.1.		X	The criterion for persistence (P) is not fulfilled. The criterion for bioaccumulation (B) is not fulfilled. The criterion for long range transport is not fulfilled
Persistent, bioaccumulative and toxic substance (PBT)				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a persistent, bioaccumulative and toxic (PBT) substance as laid out in Regulation 1107/2009 Annex II Section 3.7.2.		X	Only one of the three criteria is fulfilled: The criterion for persistence (P) is not fulfilled. The criterion for bioaccumulation is not fulfilled. The criterion for toxicity (T) is fulfilled. NOEC < 0.01 mg/L (chronic toxicity for aquatic organisms)
Very persistent and very bioaccumulative substance (vPvB).				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a a very persistent and very bioaccumulative substance (vPvB) as laid out in Regulation 1107/2009 Annex II Section 3.7.3.		X	The criterion for persistence (P) is not fulfilled. The criterion for bioaccumulation (B) is not fulfilled.
Ecotoxicology				
		Yes	No	
	It is considered that the risk assessment demonstrates risks to be acceptable in accordance with the criteria laid down in the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) under realistic proposed conditions of use of a plant protection product containing the active substance, safener or synergist. The RMS is content that the assessment takes into account		X	The long-term risk assessment for mammals could not be finalized for the active substance for uses on maize and lettuce (based on Tier 1 TER values): - The long-term risk for the small herbivorous mammal (common vole) needs to be refined for use on maize. - The long-term risk for the small insectivorous (shrew), the small omnivorous (mouse), the small herbivorous (vole) and the large

	the severity of effects, the uncertainty of the data, and the number of organism groups which the active substance, safener or synergist is expected to affect adversely by the intended use.			herbivorous (lagomorph) needs to be refined for the use on lettuce. The risk of the active substance indoxacarb for earthworm eating mammal also needs to be refined (Tier 1 TER values below the trigger) for uses on maize and lettuce. The risk via secondary poisoning (consumption of earthworms and fish) for birds and mammals is not finalized for the metabolites of indoxacarb for uses on maize and lettuce (Refer to level 2, section 2.9.9).
	It is considered that, on the basis of the assessment of Community or internationally agreed test guidelines, the substance **HAS** endocrine disrupting properties that may cause adverse effects on non-target organisms.		X	No indications for potential for endocrine disrupting properties were found.
	Linked to the consideration of the endocrine properties immediately above. It is considered that the exposure of non-target organisms to the active substance in a plant protection product under realistic proposed conditions of use is negligible.			
	It is considered that it is established following an appropriate risk assessment on the basis of Community or internationally agreed test guidelines, that the use under the proposed conditions of use of plant protection products containing this active substance, safener or synergist: — will result in a negligible exposure of honeybees, or — has no unacceptable acute or chronic effects on colony survival and development, taking into account effects on honeybee larvae and honeybee behaviour.	X		Significant effects on the brood development are expected when the product is applied on a flowering crop. Negligible exposure is expected for the use on lettuce as applications are intended before flowering. It is recommended not to apply during flowering for the use on maize. Strong effects on the colony are also expected when the product is sprayed in the presence of honeydew. It is recommended not to apply during honeydew production periods.
Residue definition				
		Yes	No	
	It is considered that, where relevant, a residue definition can be established for the purposes of risk assessment and for enforcement purposes.	X		The residue definition for enforcement and risk assessment in all plant commodities is proposed as the sum of indoxacarb and its R enantiomer. The submitted information on the metabolism in livestock is considered sufficient to propose a residue definition for animal products: • the sum of indoxacarb and its R enantiomer for enforcement in all commodities of animal origin; • the sum of indoxacarb and its R enantiomer for risk assessment in

				ruminants and pigs; • the sum of indoxacarb, its R enantiomer and its N-decarboxylated metabolite (IN-JT333), expressed as indoxacarb, for risk assessment in poultry (tentative).
Fate and behaviour concerning groundwater				
		Yes	No	
	It is considered that it has been established for one or more representative uses, that consequently after application of the plant protection product consistent with realistic conditions on use, the predicted concentration of the active substance or of metabolites, degradation or reaction products in groundwater complies with the respective criteria of the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.	X		The PECgw results for indoxacarb and its major soil metabolites are <0.1 µg/L for all the representative uses. However, PECgw for metabolite IN-U8E24 should be performed when data on degradation rate and adsorption are available.

3.1.2. Proposal – Candidate for substitution

Candidate for substitution				
		Yes	No	
	It is considered that the active substance shall be approved as a candidate for substitution		X	Toxicology: No (It is to be noted that proposed reference values for indoxacarb are not significantly lower than those of the majority of active substances taking into account the threshold mentioned in the Commission document *Questions and Answers on Candidates for Substitution* Rev. 1, January 2015 in which threshold for ADI is 0.001 mg/kg bw/d, threshold for ARfD is 0.004 mg/kg bw and threshold for AOEL is 0.001 mg/kg bw/d). Fate and behaviour in the environnement and Ecotoxicology: No

3.1.3. Proposal – Low risk active substance

Low-risk active substances				
		Yes	No	
	It is considered that the active substance **shall be considered of low risk.** In particular it is considered that the substance **should NOT be classified or proposed for classification** in accordance with Regulation (EC) No 1272/2008 as at least one of the following: — carcinogenic, — mutagenic, — toxic to reproduction, — sensitising chemicals, — very toxic or toxic, — explosive, — corrosive. In addition it is considered that **the substance is NOT**: — persistent (half-life in soil more than 60 days), — has a bioconcentration factor higher than 100, — is deemed to be an endocrine disrupter, or — has neurotoxic or immunotoxic effects.		X	The active substance is considered very toxic to aquatic life with long lasting effects: Aquatic acute 1; H400 Aquatic chronic 1; H410 The active substance is a sensitising compound and is considered toxic (including neurotoxic effects): STOT RE 1 H372 (blood, nervous system, heart) Skin Sens 1B H317 Acute Tox 3 H301 Acute Tox 4 H332

3.1.4. List of studies to be generated, still ongoing or available but not peer reviewed

Data gap	Relevance in relation to representative use(s)	Study status		
		No confirmation that study available or on-going.	Study on-going and anticipated date of completion	Study available but not peer-reviewed
3.1.4.1. Identity of the active substance or formulation				
For the active substance, the inactive isomer and some impurities, the certified values are not relied on the values given in the profile of batches and compared with the QC data from improved manufacturing process. RMS proposed to raise the minimum content of the active substance in technical indoxacarb to 93% and reviewing specifications for some impurties (see Volume 4).	Relevant for all representative uses.	X		
3.1.4.2. Physical and chemical properties of the active substance and physical, chemical and technical properties of the formulation				
Tests for explosivity, flammability, self ignition and oxidising properties of the active substance should be performed according to CLP criteria (manual UN RTDG)	Relevant for all representative uses.	X		
Tests for explosivity, flammability, self ignition, oxidising properties and flash point for formulation product should be performed according to CLP criteria (manual UN RTDG)	Relevant for all representative uses.	X		
Relevant impurities content in the formulation should be determined before and after storage study or a justification for "non-formation" of	Relevant for all representative uses.	X		

these impurities during the formulation or the storage is required.				
3.1.4.3. Data on uses and efficacy				
No further studies required				
3.1.4.4. Data on handling, storage, transport, packaging and labelling				
No further studies required				
3.1.4.5. Methods of analysis				
Extraction efficiency in different solvent systems used in monitoring studies for determination of indoxacarb in all types of matrices (plants and food of animal origin) must be demonstrated in details.	Relevant for all representative uses.	X		
- ILV of analytical method (S.Richter, 2013, report DuPont 39006) for determination of residues in product of animal origin is required. Additionally, no validation data were provided for fat. Thus main method and ILV are required for fat matrix. **Or** - ILV of analytical method (J.J Stry, 2004, report DuPont 12739 Rev1) for determination of residues in skin, liver, muscle, fat and eggs is required. Additionally, no validation data were provided for milk. Thus main method and ILV are required for milk matrix.	Relevant for all representative uses.	X		
Specificity of the method (Linkerhagner, M., Guinivan, R.A. 2001) is required	Relevant for all representative uses.	X		

A confirmatory method for determination of indoxacarb residue in Body fluids and tissues must be provided.	Relevant for all representative uses.	X		
3.1.4.6. Toxicology and metabolism				
Comparative *in vitro* metabolism study with the active substance	Relevant for all representative uses.	X		
Short-term repeated dose toxicity study with the residue metabolite IN-JT333	Relevant for all representative uses.	X		
Genotoxicity data on impurity [redacted]	Relevant for all representative uses.	X		
Safety data sheets of starting materials according to EU requirements	Relevant for all representative uses.	X		
3.1.4.7. Residue data				
An analytical method for enforcement of the proposed residue definition in dry commodities.	Relevant for representative use on maize (silage/forage)	X		
A valid storage stability study in maize forage	Relevant for representative use on maize (silage/forage)	X		
3.1.4.8. Environmental fate and behaviour				
Studies on degradation rate under aerobic conditions and adsorption should be performed for metabolite IN-U8E24.	Relevant for all representative uses.	X		
Further investigation should be done on the identity of metabolite IN-ML437-OH and on the identification and characterization of the unidentified polar fraction from the study of Singles (2002). This could be addressed with an additional soil metabolism study with active isomer DPX-KN128 on similar soil, with correct mass balance and peaks identification, to confirm	Relevant for all representative uses.	X		

residue definition for risk assessment.				
Information on the effect of water treatment processes on the nature of indoxacarb residues when surface water or groundwater are abstracted for drinking water should be provided. It is however noticeable that no guidance to address this issue is available	Relevant for all representative uses.	X		
3.1.4.9. Ecotoxicology				
IN-KG433: Acute toxicity with an additional invertebrate species	Relevant for all representative uses	X (According to applicant, a study has been scheduled)		

3.1.5. Issues that could not be finalised

An issue is listed as an issue that could not be finalised where 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, as laid out in Commission Regulation (EU) No 546/2011, and where 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).

Area of the risk assessment that could not be finalised on the basis of the available data	Relevance in relation to representative use(s)
Genotoxicity data on impurity [redacted]	Relevant for all representative uses
A risk assessment for groundwater shall be performed for metabolite IN-U8E24 when data on degradation rate and and soil adsorption are available.	Relevant for all representative uses
Long-term risk assessment for mammals (further considerations needed to address the potential risk to mammals)	Relevant for all representative uses
Risk assessment for birds and mammals via secondary poisoning for metabolites (further data needed to address the potential risk via secondary poisoning for the metabolites of indoxacarb)	Relevant for all representative uses
Risk assessment for mammals via secondary poisoning for indoxacarb (further considerations needed to address the potential risk of indoxacarb for earthworms eating mammals)	Relevant for all representative uses
Risk assessment for aquatic invertebrates of metabolite IN-KG433	Relevant for all representative uses

3.1.6. Critical areas of concern

An issue is listed as a critical area of concern:
(a) where the substance does not satisfy the criteria set out in points 3.6.3, 3.6.4, 3.6.5 or 3.8.2 of Annex II of Regulation (EC) No 1107/2009 and the applicant has not provided detailed evidence that the active substance is necessary to control a serious danger to plant health which cannot be contained by other available means including non-chemical methods, taking into account risk mitigation measures to ensure that exposure of humans and the environment is minimised, or
(b) where there is enough information available to perform an assessment for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) 546/2011, and where this assessment does not permit to conclude 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 where the assessment at a higher tier level could not be finalised due to a lack of information, and where the assessment performed at the lower tier level does not permit

to conclude 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.

Critical area of concern identified	Relevance in relation to representative use(s)
Acute Risk assessment for consumer is not acceptable	Use on lettuce
Risk for workers	Use on lettuce According to EUROPOEM: unacceptable risk considering 4 applications in lettuce (intended GAP). No unacceptable risk if the maximum number of applications is restricted to 2.

3.1.7. Overview table 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 3.3.1, has been evaluated as being effective, then 'risk identified' is not indicated in this table.)
All columns are grey as the material tested in the toxicological studies has not been demonstrated to be representative of the technical specification.

Note: RMS proposes new technical specifications according to the new manufacturing process. These new proposed specifications are not totally covered by the toxicological and ecotoxicological risk assessment (please refer to tables 3.1.4 and 3.1.5).

Representative use		Use "Maize" (X^1)	Use "Lettuce" (X^1)
Operator risk	Risk identified	*	*
	Assessment not finalised		
Worker risk	Risk identified		X** *
	Assessment not finalised		
Bystander risk	Risk identified	*	*
	Assessment not finalised		
Consumer risk	Risk identified		X
	Assessment not finalised		
Risk to wild non target terrestrial vertebrates	Risk identified		
	Assessment not finalised	X	X
Risk to wild non target terrestrial organisms other than vertebrates	Risk identified	Mitigation measures necessary	Mitigation measures necessary
	Assessment not finalised		
Risk to aquatic	Risk identified		

organisms	Assessment not finalised	X	X
Groundwater exposure active substance	Legal parametric value breached		
	Assessment not finalised		
Groundwater exposure metabolites	Legal parametric value breached		
	Parametric value of 10µg/L[(a)] breached		
	Assessment not finalised	X (No PECgw for metabolite IN-U8E24)	X (No PECgw for metabolite IN-U8E24)
Comments/Remarks			

The superscript numbers in this table relate to the numbered points indicated within chapter 3.1.5 and 3.1.6. Where there is no superscript number, see level 2 for more explanation.

(a): Value for non relevant metabolites prescribed in SANCO/221/2000-rev 10-final, European Commission, 2003

* The risk is not acceptable for operators after an acute exposure (all uses), for child bystanders and child residents (all uses) and for workers (use on lettuce) according to the EFSA model (2014). However, this model will apply to applications submitted from 1 January 2016 which is not the case for the renewal dossier of Indoxacarb.

** Unacceptable risk considering 4 applications in lettuce. No unacceptable risk if the maximum number of applications is restricted to 2.

3.1.8. Area(s) where expert consultation is considered necessary

It is recommended to organise a consultation of experts on the following parts of the assessment report:

Area(s) where expert consultation is considered necessary	Justification
None	*N.A.*

3.1.9. Critical issues on which the Co RMS did not agree with the assessment by the RMS

Points on which the co-rapporteur Member State did not agree with the assessment by the rapporteur member state. Only the points relevant for the decision making process should be listed.

Issue on which Co-RMS disagrees with RMS	Opinion of Co-RMS	Opinion of RMS
Carcinogenic potential of the active substance	**ES (Co-RMS):** The toxicokinetics and overall metabolism of DPX MP062 and DPX JW062 showed quantitative differences; moreover, according to the available data DPX-MP062 (75:25) seems to be more absorbed in female rats than DPX-JW062 (50:50). From a theoretical point of view, the greater amount of	The RMS acknowledged that carcinogenicity studies were only performed with the racemic mixture DPX-JW062 (50:50). Nevertheless, given that: - no neoplastic lesions were observed in the rat and mouse long-term studies with DPX-JW062 (50:50);

	the S-isomer in DPX-KN128 would lead to an increase of metabolite IN-JT333 and consequently prolonged and more markedly effects in female rats could be expected. In view of the available data for long-term and carcinogenesis (there are only studies with the 50:50 proportion of the enantiomers) **the carcinogenic potential of indoxacarb can´t totally excluded given the higher proportion of S-enantiomer in DPX-KN128**	- DPX-KN128 (99:1) and DPX-MP062 (75:25) did not show genotoxic potential; - the metabolite IN-JT333 did not show genotoxic potential; - DPX-JW062 (50:50), DPX-MP062 (75:25) and DPX-KN128 (99:1) showed similar adverse effects at similar range of dose levels. No additional target organ was identified with the pure enantiomer DPX-KN128; it is considered unlikely that DPX-KN128 would be a carcinogenic substance.

3.2. PROPOSED DECISION

[redacted]

[redacted]

3.3. RATIONAL FOR THE CONDITIONS AND RESTRICTIONS TO BE ASSOCIATED WITH THE APPORVAL OR AUTHORISATION(S), AS APPROPRIATE

[redacted]

3.4. APPENDICES

GUIDANCE DOCUMENTS USED IN THIS ASSESSEMENT

SANCO/2012/11251 rev.1.2: Guidance Document on the renewal of approval of active substances to be assessed in compliance with Regulation (EU) No 844/2012 (the Renewal Regulation)

EFSA Guidance on Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009. EFSA Journal 2011;9(2):2092.

Section identity, physical chemical and analytical methods

SANCO/3030/99 rev.4: Technical Material and preparations: guidance for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex II (part A, Section 4) and Annex III (part A, Section 5) of Directive 91/414

SANCO/3029/99 rev .4: Residues: guidance for generating and reporting methods of analysis in support of pre-registration data requirements for Annex II (part A, section 4) and Annex III (part A, Section 5) of directive 91/414

SANCO/825/00 rev.8.1: Guidance document on pesticide residues analytical methods

Section Toxicology

EFSA Panel on Plant Protection Products and their Residues (PPR); Guidance on Dermal Absorption. EFSA Journal 2012;10(4):2665. [30 pp.] doi:10.2903/j.efsa.2012.2665

Guidance on the Assessment of the Relevance of Metabolites in Groundwater of Substances Regulated Under Council Directive 91/414/EEC, SANCO/221/2000-Rev 10 (2003)

Guidance document on the assessment of the equivalence of technical materials of substances regulated under Regulation (EC) No 1107/2009. SANCO/10597/2003-rev. 10.1 (2012)

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.

ECHA Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, version 4.1 June 2015.

EFSA Scientific Committee; Scientific Opinion on the applicability of the Margin of Exposure approach for the safety assessment of impurities which are both genotoxic and carcinogenic in substances added to food/feed. EFSA Journal 2012;10(3):2578.

Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874

Section Residue and consumer risk assessment

FAO (Food and Agriculture Organization of the United Nations), 2009. Submission and evaluation of pesticide residues data for the estimation of Maximum Residue Levels in food and feed**.** Pesticide Residues. 2nd Ed. FAO Plant Production and Protection Paper 197, 264 pp.

OECD, 2007, OECD Guidelines for the testing of chemicals – Metabolism in crops. No. 501, OECD, Paris 2007.

OECD, 2007, OECD Guidelines for the testing of chemicals – Metabolism in rotational crops. No 502, Paris 2007.

OECD, 2007, OECD Guidelines for the testing of chemicals – Metabolism in livestock, No. 503, OECD, Paris 2007.

OECD, 2007, OECD Guidelines for the testing of chemicals – Residues in rotational crops (limited field studies). No 504, Paris 2007.

OECD, 2007. OECD Guidelines for the testing of chemicals – Stability of pesticide residues in stored commodities. No 506, OECD, Paris 2007.

OECD, 2007. OECD Guidelines for the testing of chemicals – Nature of the pesticide residues in processed commodities, high temperature hydrolysis. No 507, Paris 2007.

OECD, 2008. OECD Guidelines for the testing of chemicals – Magnitude of pesticide residues in processed commodities. No 508, Paris 2008.

OECD, 2009. OECD Guidelines for the testing of chemicals – Crop field trial. No 509, Paris 2009

Section fate and behavour in environmenent

FOCUS (1997). Soil Persistence Models and EU Registration, European Commission Document No. 7617/VI/96. 29.2.97.

FOCUS (2006) "Guidance Document on Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration" Report of the FOCUS Work Group on Degradation Kinetics, EC Document Reference Sanco/10058/2005 version 2.0, 434 pp

European Food Safety Authority, 2014. EFSA Guidance Document for evaluating laboratory and field dissipation studies to obtain DegT50 values of active substances of plant protection products and transformation products of these active substances in soil. EFSA Journal 2014;12(5):3662, 37 pp., doi:10.2903/j.efsa.2014.3662

FOCUS (2000) FOCUS Groundwater Scenarios in the EU Review of Active Substances. Report of the FOCUS Groundwater Scenarios Workgroup. EC Document Reference Sanco/321/2000 rev.2, 202 pp.

FOCUS (2002) Generic Guidance for FOCUS groundwater scenarios. Version 1.1

FOCUS (2009) Assessing Potential for Movement of Active Substances and their Metabolites to Ground Water in the EU. Report of the FOCUS Ground Water Work Group, EC Document Reference Sanco/13144/2010 version 1, 604 pp.

European Commission (2014) "Assessing Potential for Movement of Active Substances and their Metabolites to Ground Water in the EU" Report of the FOCUS Ground Water Work Group, EC Document Reference Sanco/13144/2010 version 3, 613 pp.

FOCUS (2014) Generic Guidance for Tier 1 FOCUS Ground Water Assessments. Version 2.2. May 2014.

Guidance on the Assessment of the Relevance of Metabolites in Groundwater of Substances Regulated Under Council Directive 91/414/EEC, SANCO/221/2000-Rev 10 (2003)

FOCUS (2003) FOCUS Surface Water Scenarios in the EU Evaluation Process under 91/414/EEC Review of Active Substances. Report of the FOCUS Working Group on Surface Water Scenarios. EC Document Reference Sanco/4802/2001 rev.2, 245 pp.

FOCUS (2012) Generic guidance for FOCUS surface water Scenarios, version 1.1. Up-to-date version controlled document to Sanco/4802/2001 rev.2.

FOCUS (2007a). "Landscape And Mitigation Factors In Aquatic Risk Assessment. Volume 1. Extended Summary and Recommendations". Report of the FOCUS Working Group on Landscape and Mitigation Factors in Ecological Risk Assessment, EC Document Reference SANCO/10422/2005 v2.0. 169 pp.

FOCUS (2007b). "Landscape And Mitigation Factors In Aquatic Risk Assessment. Volume 2. Detailed Technical Reviews". Report of the FOCUS Working Group on Landscape and Mitigation Factors in Ecological Risk Assessment, EC Document Reference SANCO/10422/2005 v2.0. 436 pp.

FOCUS (2008) "Pesticides in Air: Considerations for Exposure Assessment". Report of the FOCUS Working Group on Pesticides in Air, EC Document Reference SANCO/10553/2006 Rev 2 June 2008. 327 pp.

Section ecotoxicology

EFSA (European Food Safety Authority), 2009. Guidance Document on Risk Assessment for Birds and Mammals on request of EFSA. EFSA Journal 2009; 7(12):1438.

EPPO/OEPP (2001) EPPO Standards PP1/170(3) Test methods for evaluating the side –effects of plant protection products on honey bees. Bulletin OEPP/EPPO Bulletin 31, 323-330

European Commission, 2002. Guidance Document on Terrestrial Ecotoxicology Under Council Directive 91/414/EEC. SANCO/10329/2002 rev.2 final, 17 October 2002.

European Commission, 2002. Guidance Document on Aquatic Ecotoxicology Under Council Directive 91/414/EEC. SANCO/3268/2001 rev 4 (final), 17 October 2002.

Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters" (EFSA Panel on Plant Protection Products and their Residues, 2013, EFSA Journal 2013;11(7):3290

SETAC (Society of Environmental Toxicology and Chemistry), 2001. Guidance Document on Regulatory Testing and Risk Assessment procedures for Plant Protection Products with Non-Target Arthropods. ESCORT 2.

3.5. REFERENCE LIST

Indoxacarb - Commission review report: Indoxacarb SANCO/1408/2001 – rev.3, dated on 23 September 2005.

Indoxacarb - EFSA review of the existing MRLs: EFSA Journal 2011;9(8):2343)

Indoxacarb – Post-inclusion Addendum 1, Volume 3 (B6) Annex B, The Netherlands, October 2007

Committee for Risk Assessment RAC - Opinion proposing harmonised classification and labelling at Community level of Indoxacarb and Indoxacarb (enantiomeric reaction mass S:R 75:25), ECHA/RAC/CLH-O-0000001735-72-01/F, Adopted 1 June 2011