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Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade

Chemical Review Committee
Seventeenth meeting
Rome (online), 20–24 September 2021
Item 4 (b) (iii) of the provisional agenda*

Technical work: review of notifications of final regulatory action: iprodione

Iprodione: notifications of final regulatory action

Note by the Secretariat

I. Introduction

1. In accordance with paragraph 5 of Article 5 of the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade, the Secretariat has received two notifications of final regulatory action for iprodione that meet the requirements of Annex I to the Convention from Parties in the following two prior informed consent regions:

(a) Africa: Mozambique (pesticide);[1]

(b) Europe: European Union (pesticide).[2]

2. The notifications from Mozambique and the European Union are set out in the annex to the present note. The supporting documentation provided by Mozambique and the European Union is set out in documents UNEP/FAO/RC/CRC.17/INF/11 and UNEP/FAO/RC/CRC.17/INF/12, respectively.

II. Proposed action

3. The Committee may wish:

(a) To review the information provided in the notifications and the supporting documentation from Mozambique and the European Union related to iprodione, in accordance with the criteria set out in Annex II to the Convention;

(b) If it concludes that the notifications meet the criteria set out in Annex II to the Convention, to recommend to the Conference of the Parties that the chemical in question be made subject to the prior informed consent procedure and, accordingly, be listed in Annex III to the Convention, and to agree on a workplan for the preparation of a draft decision guidance document on iprodione.

* UNEP/FAO/RC/CRC.17/1.

[1] See PIC Circular LI, June 2020.

[2] See PIC Circular L, December 2019.

Annex

Notifications of final regulatory action for iprodione

A. Notification of final regulatory action for iprodione in the pesticide category submitted by Mozambique

B. Notification of final regulatory action for iprodione in the pesticide category submitted by the European Union

ROTTERDAM CONVENTION

SECRETARIAT FOR THE ROTTERDAM CONVENTION
ON THE PRIOR INFORMED CONSENT PROCEDURE
FOR CERTAIN HAZARDOUS CHEMICALS AND PESTICIDES
IN INTERNATIONAL TRADE

UNEP

FORM FOR NOTIFICATION
OF FINAL REGULATORY ACTION TO BAN OR SEVERELY RESTRICT A CHEMICAL

Country: Mozambique

SECTION 1 IDENTITY OF CHEMICAL SUBJECT TO THE FINAL REGULATORY ACTION

1.1	**Common name**	Iprodione
1.2	**Chemical name according to an internationally recognized nomenclature (e.g. IUPAC), where such nomenclature exists**	3-(3,5-dichorophenyl)-*N*-isopropyl-2,4-dioxoimidazolidine-1-carboxamide
1.3	**Trade names and names of preparations**	Iprodione 25,5% SC
1.4	**Code numbers**	
1.4.1	CAS number	36734-19-7
1.4.2	Harmonized System customs code	380861
1.4.3	Other numbers (specify the numbering system)	(EC) 253-178-9

1.5 Indication regarding previous notification on this chemical, if any

1.5.1 ☒ This is a first time notification of final regulatory action on this chemical.

1.5.2 ☐ This notification replaces all previously submitted notifications on this chemical.
Date of issue of the previous notification: _____

SECTION 2 FINAL REGULATORY ACTION

2.1 The chemical is: ☒ **banned** **OR** ☐ **severely restricted**

2.2 Information specific to the final regulatory action

2.2.1 Summary of the final regulatory action

Based on the decision Nr. 001/DNSA/2014 Iprodione was banned by the National Directorate of Agrarian Services from further import and use in Mozambique. The ban of all uses and the cancellation of the products containing Iprodione in the country was decided due to the toxic nature and hazardous properties of this active substance which combined with the improper use in the country due to the local specific conditions of use can damage human and animal health. The decision to ban the registration of the Iprodione was taken as the last step of the project for risk reduction of highly hazardous pesticides which identified highly hazardous pesticides that are registered in Mozambique. After consultations with different actors (public sector, private sector, civil society and others) cancelation of registrations and consequent ban and non-approval for their use in Mozambique was approved.

2.2.2 Reference to the regulatory document, e.g. where decision is recorded or published

Deliberacao Nr. 001/DNSA/2014 by the National Directorate of Agriculture and Agrarian Services (The Pesticide Register Authority).

2.2.3 Date of entry into force of the final regulatory action

15/07/2014

2.3 Category or categories where the final regulatory action has been taken

2.3.1 All use or uses of the chemical in your country prior to the final regulatory action

Used as fungicide in vines, fruits trees and vegetables.

2.3.2 Final regulatory action has been taken for the category ☐ Industrial

Use or uses prohibited by the final regulatory action

N/A

Use or uses that remain allowed (only in case of a severe restriction)

N/A

2.3.3 Final regulatory action has been taken for the category ☒ Pesticide

Formulation(s) and use or uses prohibited by the final regulatory action

Ban all formulation and for all uses.

Formulation(s) and use or uses that remain allowed

(only in case of a severe restriction)

None

2.4 **Was the final regulatory action based on a risk or hazard evaluation?**

☒ **Yes**

☐ **No** (If no, you may also complete section 2.5.3.3)

2.4.1 If yes, reference to the relevant documentation, which describes the hazard or risk evaluation

Project document EP/MOZ/101/UEP – Reducing risk of Highly Hazardous pesticides in Mozambique

- Come A.M. & van der Valk H., 2014. Step 1 – Shortlisting highly hazardous pesticides Consultancy report undertaken under the Project EP/MOZ/101/UEP – Reducing Risks of Highly Hazardous Pesticides in Mozambique.
- Come A.M.; Dona L.L.; Mancini F. & van der Valk H., 2014. Step 2 – Survey of pesticide use practices in selected cropping systems
- FAO/WHO (2008) Report of the 2nd Joint Meeting on Pesticide Management and the 4th Session of the FAO Panel of Experts on Pesticide Management. 6-8 October 2008, Geneva. Food and Agriculture Organization of the United Nations, Rome & World Health Organization, Geneva.

http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/Code/Report.pdf

2.4.2 Summary description of the risk or hazard evaluation upon which the ban or severe restriction was based.

2.4.2.1 Is the reason for the final regulatory action relevant to human health?

☒ Yes

☐ No

If yes, give summary of the hazard or risk evaluation related to human health, including the health of consumers and workers

A project entitled Reducing Risks of Highly Hazardous Pesticides (HHPs) in Mozambique was initiated by the Government of Mozambique with the

objective to reduce the greatest risks associated with pesticide use in the country. The ultimate goal was to develop and implement an "HHP Risk Reduction Action Plan" for the most dangerous pesticides and use situations, resulting over time in the implementation of a variety of risk reduction measures based on a review of use conditions.

In the first step of the project, a review of all the pesticides registered in Mozambique was carried out and a shortlist of highly hazardous pesticides was established. This shortlist was based on an assessment of the hazards of the pesticides, based on criteria established by the FAO/WHO Joint Meeting on Pesticide Management (JMPM) (FAO/WHO, 2008).

During the second step of the project, a use survey was carried out in selected regions and cropping systems in Mozambique. The main goal of the survey was to identify the conditions under which pesticides are being used in the country and their contribution to potential risks for human health and the environment.

The third step of the project consisted of a stakeholder consultation to further discuss the use and risks of highly hazardous pesticides in Mozambique and fine-tune the shortlist based on the survey results and the expertise and experience of stakeholders.

As result, a short list of HHPs, including "coming close" to HHPs, which were used in the country, was established.

Iprodione was on the short list as a pesticide "coming close" to HHPs based on the below indicated criteria:

- Pesticides for which carcinogenicity evaluations by different registration/assessment authorities did not lead to consistent classification as GHS Category 1A or 1B, but which were, based on the evidence of one of these authorities, considered of particular concern for use in Mozambique (Come A.M.& van der Valk H., 2014).

- Iprodione was classified by the US EPA as likely to be carcinogenic. It was registered in the US. However, all residential uses were cancelled due to cancer risk concerns. Also, back packer sprayers and mixers should wear double layer PPE, masks and gloves. Iprodione was registered in the EU. The EC review from 2004, classified Iprodione in Category 2 of carcinogenicity classification. The US proposed risk mitigation measures posed significant concern for Mozambican use situation.

The final conclusion for the HHP assessment in Mozambique identified Iprodione as carcinogenic equivalent or similar to GHS Class 1A&1B, and therefore considered as "coming close" to HHPs. (Come A.M.& van

der Valk H., 2014.)

During the second phase of the project field surveys on the pesticide use and exposure were carried out.

The surveys (325 subsistence farmers interviewed) revealed that most of the farmers applied pesticides (95%), and that the conditions of use were likely to result in undue (excessive) exposure. Half of the farmers interviewed never received any training on pesticides use, and even the other half that did, often lacked understanding of the risks involved. Farmers were spraying vegetable crops at least 14 times per growing season. One out of three applications was involving one of the HHP containing formulation (Farmers using HHPs includes almost 30% of the interviewed farmers).

Also almost none of the farmers (93%) owned or wore adequate PPE having only one or no protective items at all. Only 2% of those applying HHPs wore adequate full body protection PPE. About half of the farmers had not received any training on the use of pesticides. The majority of pesticide applicators used manual sprayer (36%), followed by electric sprayer (with batteries); 33% and followed by inappropriate equipment such as watering can (13.5%) or other (unknown) means (12.5%). Approximately about half of the farmers surveyed reported that they noticed to receive pesticide on their clothes, bare skin or eyes when using pesticides. The main health symptoms associated with pesticide use by farmers noticing symptoms were headaches, skin rashes, burning eyes, vomiting, burning nose, blurred vision, dizziness and excessive sweating. Almost half of the farmers declared they did not read pesticide labels, including use instructions such as proper dosage and protective measures, the main reason being illiteracy. One out of four farmers poorly understood the hazard colour band on pesticide labels that indicates acute toxicity.

The survey results showed that the use of pesticides in general, and of HHPs in particular, was likely to result in excessive exposure of farmers in Mozambique. Therefore enforcing risk mitigation measures depending solely on wearing the appropriate PPE under the local conditions of use to be difficult and unlikely to give results.

Iprodione and the products containing this a.i. were considered as harmful for the human health taking into consideration of the local conditions of use in Mozambique requiring risk mitigation measures. Therefore, the authorities decided to ban the a.i. iprodione from future use in the country and to cancel the registration of all the products

containing it.

Expected effect of the final regulatory action

Reducing the risk posed by the use of HHPs in Mozambique specially Iprodione in the context of human health.

2.4.2.2 Is the reason for the final regulatory action relevant to the environment? ☐ Yes ☒ No

If yes, give summary of the hazard or risk evaluation related to the environment

N/A

Expected effect of the final regulatory action

N/A

2.5 Other relevant information regarding the final regulatory action

2.5.1 Estimated quantity of the chemical produced, imported, exported and used

	Quantity per year (MT)	Year
produced	N/A	N/A
imported	12 L	2013
exported	N/A	N/A
used		

2.5.2 Indication, to the extent possible, of the likely relevance of the final regulatory action to other states and regions

Countries with similar conditions as well as where the farmers use pesticides without protective equipment could make similar decision in order to protect their population human health.

2.5.3 Other relevant information that may cover:

2.5.3.1 Assessment of socio-economic effects of the final regulatory action

N/A

2.5.3.2 Information on alternatives and their relative risks, e.g. IPM, chemical and non-chemical alternatives

The Ministry of Agriculture and Food Security engaged with the producer association to assess alternative fungicide options promoting the use of bio-pesticide on vegetables pest control.

2.5.3.3 Basis for the final regulatory action if other than hazard or risk evaluation

N/A

2.5.3.4 Additional information related to the chemical or the final regulatory action, if any

None

SECTION 3 PROPERTIES

3.1 Information on hazard classification where the chemical is subject to classification requirements

International classification systems **e.g. WHO, IARC, etc.**	**Hazard class**
WHO	Class III (Slightly hazardous)
GHS Hazard statements	**Category 5** ➢ H351: Suspected of causing cancer [Warning Carcinogenicity] ➢ H400: Very toxic to aquatic life [Warning Hazardous to the aquatic environment, acute hazard] ➢ H410: Very toxic to aquatic life with long lasting effects [Warning Hazardous

	to the aquatic environment, long-term

Other classification systems e.g. EU, USEPA	Hazard class
USEPA	Likely to be Carcinogenic to Humans

3.2 Further information on the properties of the chemical

3.2.1 Description of physico-chemical properties of the chemical

Isomerism: A structural isomer (RP-30228) exists which is also a major metabolite

Chemical formula: C13H13Cl2N3O3

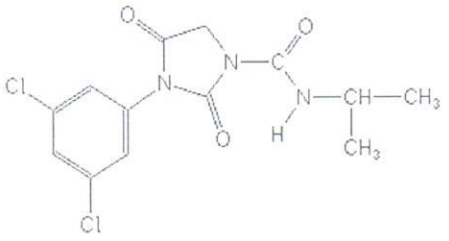
Canonical SMILES:
CC(C)NC(=O)N1CC(=O)N(C1=O)C2=CC(=CC(=C2)Cl)Cl

Isomeric SMILES: No data

International Chemical Identifier key (InChIKey): ONUFESLQCSAYKA UHFFFAOYSA-N

International Chemical Identifier (InChI): InChI=1S/C13H13Cl2N3O3/c1-7(2)16-12(20)17-6-11(19)18(13(17)21)10-4-8(14)3-9(15)5-10/h3-5,7H,6H2,1-2H3,(H,16,20)

2D structure diagram:



Physical state: white, odourless, non-hygroscopic crystals.
Molecular weight: 330.17
Melting point: 136°C

Volatility:	not volatile
Vapour Pressure:	2 × 10-7mm. Hg at 20°C
Solubility at 20°C:	g/l
water	0.013
ethanol	30
acetonitrile	150
toluene	150
benzene	200
acetone	300
methlyene chloride	500

Reference

https://sitem.herts.ac.uk/aeru/ppdb/en/Reports/403.htm#none (PPDB: Pesticide Properties Data Base)

http://inchem.org/documents/jmpr/jmpmono/v077pr32.htm

3.2.2 Description of toxicological properties of the chemical

- LD50 rat (mg/kg) – 3500 (WHO, 2009)

- Iprodione has been classified as a Group B2, or "likely," human carcinogen, based on evidence of tumors in both sexes of mouse (liver) and in the male rat (Leydig cell). A Q* of 4.39 x 10-2 was used for estimating carcinogenic risk (Leydig cell). The Agency was concerned about the cancer risk and the acute dietary risk posed by exposure to iprodione. (USEPA, 1998)

- In a study of carcinogenicity in mice, iprodione was administered over 99 weeks at dietary concentrations at 0, 160, 800, or 4000 ppm. At 800 ppm, non-neoplastic lesions were seen that included hepatocellular enlargement and hypertrophy of interstitial cells in the testis. At 4000 ppm, reduced body-weight gain, increased liver weights and increased levels of alanine and aspartate transaminases were observed. An increased incidence of liver tumours in animals of each sex and an increased incidence of luteomas of the ovaries were observed at 4000 ppm. The NOAEL was 160 ppm, equal to 23 mg/kg bw per day. In a 104-week study of carcinogenicity in rats, the dietary concentrations were 0, 150, 300, or 1600 ppm of iprodione. At 300 ppm, increased liver weights, changes in the male reproductive system including an increased incidence of interstitial-cell hyperplasia in the testis, and hypertrophic changes in the adrenals of male rats were observed. At 1600 ppm, reduced body-weight gain and an increased incidence of interstitial-cell tumours of the testis were noted. The NOAEL was 150 ppm, equal to 6 mg/kg bw per day. (JMPR, 1995)

- Toxicity (PPDB)

Property	Value	Source
Mammals - Acute oral LD50 (mg kg-1)	> 2000	A5 Rat

Mammals - Dermal LD50 (mg kg-1 body weight)	> 2000	A5 Rat
Mammals - Inhalation LC50 (mg l-1)	> 5.16	A5 Rat. 4 hr (whole body)
Other Mammal toxicity endpoints	-	
ADI - Acceptable Daily Intake (mg kg-1bw day-1)	0.06	A5 Rat, SF=100
ARfD - Acute Reference Dose (mg kg-1bw day-1)	None allocated	A5
AAOEL - Acute Acceptable Operator Exposure Level (mg kg-1 bw day-1)	-	-
AOEL - Acceptable Operator Exposure Level - Systemic (mg kg^{-1}bw day^{-1})	0.3	A5 Rat, 90 day, SF=100
Dermal penetration studies (%)	0.2-12	A5 concentration dependent

Reference

The WHO recommended classification of pesticides by hazard and guidelines to classification: 2009. (World Health Organization, 2010)

https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/fs_PC-109801_1-Nov-98.pdf

http://inchem.org/documents/jmpr/jmpmono/v95pr11.htm

https://sitem.herts.ac.uk/aeru/ppdb/en/Reports/403.htm#none

3.2.3 Description of ecotoxicological properties of the chemical

Property	Value	Source
Birds - Acute LD50 (mg kg-1)	> 2000	A5 Colinus virginianus
Birds - Short term dietary (LC50/LD50)	> 5620 mg kg feed-1	A5 Colinus virginianus
Fish - Acute 96 hour LC50 (mg l-1)	3.7	A5 Lepomis macrochirus
Fish - Chronic 21 day NOEC (mg l-1)	4.1	A5 Oncorhynchus mykiss
Aquatic invertebrates - Acute 48 hour EC50 (mg l-1)	0.66	A5 Daphnia magna
Aquatic invertebrates - Chronic 21 day NOEC (mg l-1)	0.17	A5 Daphnia magna
Aquatic plants - Acute 7 day EC_{50}, biomass (mg l^{-1})	1	F3 *Lemna gibba*
Algae - Acute 72 hour EC_{50}, growth (mg l^{-1})	1.8	A5 *Raphidocelis subcapitata*

Algae - Chronic 96 hour NOEC, growth (mg l^{-1})		3.2	Q2 Unknown species	
Honeybees (*Apis* spp.)	Contact acute LD_{50} (worst case from 24 , 48 and 72 hour values - µg bee^{-1})	> 100	A5 *Apis mellifera*	
	Oral acute LD_{50} (worst case from 24 , 48 and 72 hour values - µg bee^{-1})	> 100	A5 *Apis mellifera*	

Reference

https://sitem.herts.ac.uk/aeru/ppdb/en/Reports/403.htm#none (PPDB: Pesticide Properties Data Base)

SECTION 4 DESIGNATED NATIONAL AUTHORITY

Institution	MINISTRY OF AGRICULTURE AND FOOD SECURITY
Address	Rua da Resistência Nº 1742 Maputo - Mozambique
Name of person in charge	Khalid Cassam
Position of person in charge	Technician
Telephone	+258 823071000 / +258 84468208
Telefax	+258 21 415103
E-mail address	khalidcassam@yahoo.com.br

Date, signature of DNA and official seal: 8/4/2020

ROTTERDAM CONVENTION

SECRETARIAT FOR THE ROTTERDAM CONVENTION
ON THE PRIOR INFORMED CONSENT PROCEDURE
FOR CERTAIN HAZARDOUS CHEMICALS AND PESTICIDES
IN INTERNATIONAL TRADE

FORM FOR NOTIFICATION
OF FINAL REGULATORY ACTION TO BAN OR SEVERELY RESTRICT A CHEMICAL

Country:

European Union Member States are: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom

SECTION 1 IDENTITY OF CHEMICAL SUBJECT TO THE FINAL REGULATORY ACTION

1.1	**Common name**	Iprodione
1.2	**Chemical name according to an internationally recognized nomenclature (e.g. IUPAC), where such nomenclature exists**	3-(3,5-dichlorophenyl)-N-isopropyl-2,4-dioxoimidazolidine-1-carboxamide
1.3	**Trade names and names of preparations**	Rovral WG (BAS 610 06 F)

1.4	**Code numbers**	
1.4.1	CAS number	36734-19-7
1.4.2	Harmonized System customs code	293321
1.4.3	Other numbers (specify the numbering system)	EC: 253-178-9 CIPAC: 278 Combined Nomenclature (CN) code of the European Union: 2933 21 00

1.5 Indication regarding previous notification on this chemical, if any

1.5.1 ☒ This is a first time notification of final regulatory action on this chemical.

1.5.2 ☐ This notification replaces all previously submitted notifications on this chemical.
Date of issue of the previous notification: _____

SECTION 2 FINAL REGULATORY ACTION

2.1 The chemical is: ☒ **banned** **OR** ☐ **severely restricted**

2.2 Information specific to the final regulatory action

2.2.1 Summary of the final regulatory action

It is prohibited to place on the market or use plant protection products containing iprodione. Iprodione is not included in the list of approved active substances under Regulation (EC) No 1107/2009. As a consequence, iprodione is not approved for placing on the market pursuant to Regulation (EC) No 1107/2009 concerning the placing of plant protection products on the market. Placing on the market of plant protection products containing iprodione as active substance is prohibited as of 6 March 2018. Disposal, storage, placing on the market and use of existing stocks of plant protection products containing iprodione is prohibited as of 6 June 2018.

2.2.2 Reference to the regulatory document, e.g. where decision is recorded or published

Commission Implementing Regulation (EU) 2017/2091 of 14 November 2017 concerning the non-renewal of approval of the active substance iprodione, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending Commission Implementing Regulation (EU) No 540/2011

http://data.europa.eu/eli/reg_impl/2017/2091/oj

2.2.3 Date of entry into force of the final regulatory action

Complete entry into force of all provisions of Regulation (EU) No 2017/2091 of 14 November 2017 concerning the non-renewal of approval of the active substance iprodione, in accordance with Regulation (EC) No 1107/2009 was 4 December 2017.

2.3 Category or categories where the final regulatory action has been taken

2.3.1 All use or uses of the chemical in your country prior to the final regulatory action

Iprodione was used as a fungicide.

2.3.2 Final regulatory action has been taken for the category ☐ Industrial

Use or uses prohibited by the final regulatory action

Not relevant

Use or uses that remain allowed (only in case of a severe restriction)

Not relevant

2.3.3 Final regulatory action has been taken for the category ☒ Pesticide

Formulation(s) and use or uses prohibited by the final regulatory action

All applications as a plant protection product

Formulation(s) and use or uses that remain allowed
(only in case of a severe restriction)

Not relevant

2.4 Was the final regulatory action based on a risk or hazard evaluation?

☒ **Yes**

☐ **No** (If no, you may also complete section 2.5.3.3)

2.4.1 If yes, reference to the relevant documentation, which describes the hazard or risk evaluation

The evaluation of the active substance iprodione, following the submission of an application to renew its approval for use in plant protection products, was made in the context of the work provided for in Articles 7 to 13 of Regulation (EC) No 1107/2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC.

A Member State was designated to undertake a hazard and risk assessment based on the information submitted by the applicant and to establish a draft assessment report, which was subject to peer review during which the European Food Safety Authority (EFSA) undertook consultations with experts from Member States as well as with the applicant.

Based on the results of the evaluation, the European Commission established a review report, which was finalised in the Standing Committee on Plants, Animals, Food and Feed (PAFF Committee). The PAFF Committee concluded that no plant protection product containing the active substance iprodione is expected to satisfy in general the requirements laid down in Article 29(1) of Regulation (EC) No 1107/2009 and the uniform principles laid down in Regulation (EC) 546/2011. Therefore, iprodione should not be approved in accordance with Regulation (EC) No 1107/2009.

Peer review of the pesticide risk assessment of the active substance iprodione. European Food Safety Authority. EFSA Journal 2016;14(11):4609. (See Appendix A for substance properties)

Final Renewal report for the active substance iprodione finalised in the Standing Committee on Plants, Animals, Food and Feed at its meeting on 6 October 2017 in view of the non-renewal of the approval of XXX as active substance in accordance with Regulation (EC) No 1107/2009

2.4.2 Summary description of the risk or hazard evaluation upon which the ban or severe restriction was based.

2.4.2.1 Is the reason for the final regulatory action relevant to human health? ☒ Yes ☐ No

If yes, give summary of the hazard or risk evaluation related to human health, including the health of consumers and workers

It was concluded that no plant protection product containing the active substance iprodione is expected to satisfy in general the requirements laid down in Article 29(1) of Regulation (EC) No 1107/2009 and the uniform principles laid down in Regulation (EC) 546/2011.

According to the evaluation related to human health the following concerns were identified:

- the genotoxic potential of metabolite RP 30228 (found as a residue and impurity in the technical material) that cannot be excluded and for which the setting of reference values cannot be confirmed based on the information available. It is noted that metabolite RP 30228 is predicted to occur in groundwater above 0.1 µg/L in one FOCUS GW scenario according to the representative uses.
- Iprodione has currently harmonised classification as carcinogenic category 2. The pesticide peer review considers more appropriate classification as carcinogenic category 1B and toxic for reproduction category 2. On this basis the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine disrupting properties are met leading to a critical area of concern. This is supported by the available scientific evidence where iprodione is shown to be antiandrogenic compound and has adverse effects on different endocrine organs at the dose levels triggering the LOAEL in several toxicity studies.
- For the representative uses considered, residue levels exceed the default value as referred to in point (b) of Article 18(1) of Regulation (EC) No 396/2005 (on maximum residue levels of pesticides in or on food and feed of plant and animal origin). Consequently, the requirement set out in Points 3.6.3 and 3.6.5 of Annex II to Regulation (EC) No 1107/2009 is not fulfilled.
- an acute consumer risk that cannot be excluded based on a preliminary risk assessment. The assessment is likely to underestimate the exposure to the metabolite 3,5-dichloroaniline due to instability of the compound in residue sample storage and of residues not fully considered due

to different data gaps. Moreover, possible common toxicological effects of 3,5-dichloroaniline and iprodione and similar metabolites have not been considered in the risk assessment.

The information available is insufficient to satisfy the requirements set out in Article 4(1) to (3) of Regulation (EC) No 1107/2009, in particular with regard to:
- operator exposure estimates that according to the supported indoor uses in lettuce could not be finalised;
- the dietary consumer risk assessment in terms of food of plant and animal origin that could not be finalised given numerous data gaps identified that do not permit the establishment of final residue definitions for risk assessment.

Expected effect of the final regulatory action

Reduction of risk for the human health from the use of plant protection products containing iprodione.

2.4.2.2 Is the reason for the final regulatory action relevant to the environment? ☒ Yes ☐ No

If yes, give summary of the hazard or risk evaluation related to the environment

It was concluded that no plant protection products containing the active substance iprodione is expected to satisfy in general the requirements laid down in Article 29(1) of Regulation (EC) No 1107/2009 and the uniform principles laid down in Regulation (EC) 546/2011.

According to the evaluation related to environment the following concerns were identified:
- the predicted concentrations in groundwater that exceed 0.1 µg/L for relevant metabolites RP 35606 and RP 30181. Metabolite RP 35606 also exceeds 0.75 µg/L, in acidic soils, and metabolite RP 30181 exceeds 0.75 µg/L in both acidic and slightly acidic to alkaline soils for both intended uses (carrots and lettuce). Iprodione is classified as carcinogen category 2 in accordance with Regulation (EC) No 1272/2008 and therefore these metabolites are considered relevant as it has not been demonstrated that they do not share the same intrinsic toxicological properties of iprodione. Furthermore, during the peer review it was proposed that iprodione should be classified as carcinogen category 1B and as toxic for reproduction category 2.
- the high long-term risk of iprodione to aquatic organisms.

The information available is insufficient to satisfy the requirements set out in Article 4(1) to (3) of Regulation (EC) No 1107/2009, in particular with regard to:
- the proposed route of degradation in soil that was incomplete since it was based only on phenyl-labelled iprodione studies. Therefore, studies on the fate and behaviour of the hydantoin moiety iprodione in soil are required to demonstrate whether metabolite RP 30181 and/or other degradation/transformation products are formed at amounts requiring further assessment or not;
- the long-term risk assessment for wild mammals for all the relevant routes of exposure that could not be finalised due to the lack of a reliable endpoint;
- further information to address the potential for endocrine disruption of iprodione in fish.

Expected effect of the final regulatory action

Reduction of risk for the environment from the use of plant protection products containing iprodione.

2.5 Other relevant information regarding the final regulatory action

2.5.1 Estimated quantity of the chemical produced, imported, exported and used

	Quantity per year (MT)	Year
produced	no information	
imported	no information	
exported	no information	
used	no information	

2.5.2 Indication, to the extent possible, of the likely relevance of the final regulatory action to other states and regions

Similar human health problems are likely to be encountered in other regions where the substance is used, particularly in developing countries.

2.5.3 Other relevant information that may cover:

2.5.3.1 Assessment of socio-economic effects of the final regulatory action

Not relevant

2.5.3.2 Information on alternatives and their relative risks, e.g. IPM, chemical and non-chemical alternatives

Not relevant

2.5.3.3 Basis for the final regulatory action if other than hazard or risk evaluation

Not relevant

2.5.3.4 Additional information related to the chemical or the final regulatory action, if any

Not relevant

SECTION 3 PROPERTIES

3.1 Information on hazard classification where the chemical is subject to classification requirements

International classification systems e.g. WHO, IARC, etc.	Hazard class

Other classification systems e.g. EU, USEPA	Hazard class
Classification of the EU according to Regulation (EC) No 1272/2008 of the European Parliament and of the Council.	Carc 2, H351 - Suspected of causing cancer. Aquatic acute 1, H400 - Very toxic to aquatic life (Acute M = 100). Aquatic chronic 1, H410 - Very toxic to aquatic life with long lasting effects (Chronic M = 100).

3.2 Further information on the properties of the chemical

3.2.1 Description of physico-chemical properties of the chemical

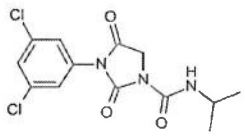
Minimum purity: 980 g/kg

FAO specification: 278/TC (July 2006) - min. 960 g/kg

Molecular formula: $C_{13}H_{13}Cl_2N_3O_3$

Molecular weight: 330.17 g/mol

Structural formula:



Appearance: Pure material: White crystalline powder (99.9%)

Technical material: White powder (95.5%)

Melting point: 134 °C (purity 99.9%)

Boiling point: Not determined, higher than the decomposition point.

Temperature of decomposition: 164.5 °C (99.7%)

Relative density: Open

Vapour pressure: 5.10^{-7} Pa at 25 °C (99.7%)

Henry's law constant: $0.7x10^{-5}$ Pa m^3 mol^{-1} (20°C)

Solubility in water:

8.9 mg/L at 20°C (pH 5) (99.8%)
6.8 mg/L at 20°C (pH 7) (99.8%)
9.0 mg/L at 30°C (pure water, pH 6.1) (99.8%)

Solubility in organic solvents:

Hexane 590 mg/L (96.1%)
Acetonitrile 168 g/L (96.1%)
Dichloromethane 450 g/L (96.1%)
Ethylacetate 22.5 g/L (96.1%)
Acetone 342 g/L (96.1%)
Toluene 147 g/L (96.1%)
1-octanol 10 g/L (96.1%)
(temperature not provided)

Partition co-efficient n-octanol/water (log Pow):

log P_{OW} = 2.99 at 25°C (pH 3) (99.7%)
log P_{OW} = 3.00 at 25°C (pH 5) (99.7%)

Surface tension: 73 mN/m at 20°C (6 mg/L) (97.7%)

UV/VIS absorption (max.) incl. ε : (solution: water)
λmax (204.5 nm); ε (44333 L mol^{-1} cm^{-1})
No λmax between 205 and 400 nm, no absorption above 330 nm.
No significant modification of the spectrum was observed in acidic medium (pH = 1) (99.9 %)

Reference

Peer review of the pesticide risk assessment of the active substance iprodione. European Food Safety Authority. EFSA Journal 2016;14(11):4609. (See Appendix A for substance properties)

3.2.2 Description of toxicological properties of the chemical

Short-term toxicity

Target organ / critical effect:
Rat: decreased body weight and food consumption, adrenals, ovary, uterus
Mouse: liver, adrenals
Dog: liver, adrenals, haematology, prostate, kidney
Relevant oral NOAEL: 1-year, dog: 17.5 mg/kg bw per day (400 ppm)
90-day, rat: 30.8 mg/kg bw per day (500 ppm)
90-day, mouse: 260 mg/kg bw per day.
Relevant dermal NOAEL: 28-day, rabbit: 1000 mg/kg bw per day

Long-term toxicity and carcinogenicity

Target organ / critical effect:
Rat: liver, adrenals, testes, epididymides, seminal vesicles, prostate, spleen
Mouse : liver, testes, non-glandular stomach, uterus, ovaries, spleen, kidney, adrenals
LOAEL = 6.1 mg/kg bw per day (2-year rat)
NOAEL = 23 mg/kg bw per day (18-month mouse)
Carcinogenicity:
Rat: interstitial Leydig cell tumours
Mouse: ovary luteomas, benign and malignant liver cell tumours
LOAEL (carcinogenicity) = 6.1 mg/kg bw per day (2-year rat)
NOAEL = 115 mg/kg bw per day (18-month mouse)

Reproductive toxicity

Reproduction toxicity

In 2-generation study:

Parental toxicity: effects on adrenals. Highest dose level: decreased body weight gain and food consumption Reproductive toxicity: sperm abnormalities
Offspring's toxicity: sperm abnormalities F1 and marginal delay in preputial separation. Highest dose levels:
persistence of areolas/nipples F1/F2, decreased bodyweight gain, decreased male anogenital distances F1/F2 In an older 2-generation study:
Parental toxicity: decreased body weight gain and food consumption
Reproductive toxicity: decreased mean number of pups per litter
Offspring's toxicity: clinical signs, decreased number of live/dead pups delivered, decreased pup survival and pup bodyweight during lactation
parental NOAEL = 26.9 mg/kg bw per day
reproductive LOAEL = 26.9 mg/kg bw per day
offspring LOAEL = 26.9 mg/kg bw per day

Developmental toxicity

Rat:
Maternal toxicity: effects on adrenals, decreased bodyweight gain
Developmental toxicity: slight effect on male anogenital distance, delayed fetal development (bodyweight and increased space between the body wall and organs)
Rabbit:
Maternal toxicity: slight decreased maternal bodyweight gain. Highest dose level: bodyweight losses, abortions, postimplantation losses
Developmental toxicity: umbilical hernia
maternal NOAEL = 20 mg/kg bw per day (rat, rabbit)
developmental LOAEL = 20 mg/kg bw per day (rat)
developmental LOAEL > 20 mg/kg bw per day (rabbit)

Other toxicological studies

Supplementary studies on the active substance:

Hepatotoxicity in the mouse:

- proliferative response in centrilobular hepatocytes at 4000 ppm for 13 or 90 days

- dose-related increase in total cytochrome P450 content and in staining of the isoforms CYP2B and CYP3A on Western blots after 3- and 14-day exposure at 4000 and 12000 ppm.

Quantification of iprodione in the plasma and testes of the rat following single oral administration (70 mg/kg bw): tissue levels of iprodione in the testes mirrored those in the whole blood and plasma, but were slightly lower than plasma levels. Iprodione in the plasma was largely protein-bound.

15- and 30-day gavage rat studies: at 600 mg/kg bw per day: decreased weight of sex organs, marked increased adrenal weight and vacuolisation, higher proliferation index of iprodione treated Leydig cells, increased FSH and LH level

14-day dietary rat study: no changes in testicular function, increased LH level, dose-dependant decreased testosterone secretion in testicular sections from treated or untreated animals by addition of iprodione to the media

Hormonal measurements in male rats: at 70 and 300 mg/kg bw per day by gavage, single dose or 14-day exposure: transient reduction in circulating testosterone levels and consequent homeostatic increase in the levels of circulating LH

Measurement of Leydig cell proliferation in male rats: 14-day exposure by gavage: dose-related significant increase in Leydig cell proliferation at 70 and 300 mg/kg bw per day, not statistically significant at 6 mg/kg bw per day

Inhibition of testosterone secretion in cultured porcine Leydig cells, reversible at the withdrawal of iprodione. Iprodione appears to modulate Leydig cell steroidogenesis at the level of cholesterol transport into mitochondria

No clear evidence of competitive binding to androgen receptors isolated from rat ventral prostate

No competition with the human androgen receptor in T47D cell line

Binding to the human androgen receptor expressed within COS-1 cells: IC50 = 86 µM (literature data)

Inhibition of androgen-dependent gene expression in the hAR-expressing MDA-kb2 cell line after DHT stimulation: IC50 = 245.9 µM, insolubility of iprodione at 300 µM (literature data)

Negative response in a transactivation assay using Chinese Hamster Ovary cells transfected with hERα and hERβ and lack of activity in the MCF7 cell proliferation assay and the Yeast Oestrogen Screen (literature data)

US-EPA EDSP Tier 1 studies:

- Aromatase assay (human recombinant): no inhibition of aromatase

- Estrogen receptor binding: no interaction of the rat uterine cytosol oestrogen receptors

- Estrogen receptor transcriptional activation (Human cell line HeLa-9903): iprodione is not an agonist of hERα

- Female pubertal assay (rat): delayed initiation and completion of vaginal opening and time to first oestrus at 300 mg/kg bw per day, decreased uterine weights and altered uterine histopathology from 150 mg/kg bw per day

- Uterotrophic assay (rat): no evidence of oestrogenic activity

- Steroidogenesis assay (human cell line H295R): inhibition of androgen steroidogenesis at 30 and 100 µM

- Androgen receptor binding (rat prostate): not performed according to OPPTS Guideline but low affinity for AR binding in the available studies (see above)

- Hershberger assay (rat): not performed according to OPPTS Guideline but available in the literature: decreased androgen-sensitive tissue weights at 100 and 200 mg/kg bw per day

- Male pubertal assay (rat): not performed according to OPPTS Guideline but available in the literature: delayed preputial separation from 100 mg/kg bw per day, decreased weights of seminal vesicles and epididymides, increased adrenals and liver weights at 200 mg/kg bw per day, decreased testosterone level at all dose level (LOAEL = 50 mg/kg bw per day) and 17α-hydroxyprogesterone and androstenedione from 100 mg/kg bw per day

Endocrine disrupting properties:

Iprodione showed endocrine disrupting properties, particularly anti-androgenic effects. Iprodione may interfere with steroidogenesis at the level of cholesterol transport but another mode of action, implying its metabolites, cannot be totally excluded.

Studies performed on metabolites or impurities:

RP30228 (Reg. No. 5079647):

Minor rat metabolite (TK rat study on iprodione).

Mice: oral LD50 >10000 mg/kg bw
Rats: oral LD50 >2500 mg/kg bw; dermal LD50 >2500 mg/kg bw
Not irritating to skin and eyes of rabbits.
Ames test: negative
MNT in vitro: positive
MNT in vivo: equivocal/marginally positive
13-week oral toxicity study in rats: LOAEL of 58/64 mg/kg bw/d (M/F) (reduced body weight gain in females).

RP36112 (Reg. No. 5079623):
Minor rat metabolite (TK rat study on iprodione).
In vitro assays:
Inhibition of testosterone secretion in cultured porcine Leydig cells at the level of steroidogenic enzymes
No androgen receptor binding in human mammary gland cancer cells
Androgen receptor binding in rat ventral prostate

RP32490 (Reg. No. 5079628):
Major rat metabolite (20% in urine) (TK rat study on iprodione).
In vitro assays:
No inhibition of testosterone secretion in cultured porcine Leydig cells
No androgen receptor binding in human mammary gland cancer cells
No androgen receptor binding in rat ventral prostate
Toxicological profile covered by iprodione.

RP25040 (Reg. No. 207099):
Minor rat metabolite (TK rat study on iprodione).
Mice: oral LD50: 1125 mg/kg bw
No skin irritation effects in rabbits.
Ames test (not acceptable): negative
In vitro assays:
No inhibition of testosterone secretion in cultured porcine Leydig cells
Androgen receptor binding in human mammary gland cancer cells
Androgen receptor binding in rat ventral prostate

RP37176 (Reg. No. 5079612):
No rat metabolite (TK rat study on iprodione).
Mice: oral LD50 >1125 mg/kg bw
Ames test (not acceptable): negative
MNT in vitro: negative

M610F007 (Reg. No. 5916256):
Ames test: negative
MNT in vitro: negative
Toxicological profile covered by 3,5-DCA.

RP36221 (Reg. No. 5079618):
No rat metabolite (TK rat study on iprodione).
Rats: oral LD50 >2000 mg/kg
Ames test: negative
MNT in vitro: negative
MLA: negative

RP36115 (Reg. No. 5079624):
Rat metabolite (8% in urine) (TK rat study on iprodione).

In vitro assays:
Inhibition of testosterone secretion in cultured porcine Leydig cells at the level of cholesterol transport
No androgen receptor binding in human mammary gland cancer cells
Androgen receptor binding in rat ventral prostate
RP36114 (Reg. No. 5079627):
Major rat metabolite (11% in urine) (TK rat study on iprodione).
In vitro assays:
No androgen receptor binding in human mammary gland cancer cells
No androgen receptor binding in rat ventral prostate
RP44247 (Reg. No. 89517):
No rat metabolite (TK rat study on iprodione).
Ames test: negative
MNT in vitro: negative
RP32596 (3,5-DCA, Reg. No. 85831):
No rat metabolite (TK rat study on iprodione).
Ames test: negative
MLA: negative
MNT in vivo in mice: negative
MNT in vivo in rats (limited validity): negative
28-day oral gavage study in Wistar rats: NOAEL of 7.5 mg/kg bw/d
90-day oral gavage study in SD rats: NOAEL of 1.0 mg/kg bw/d (LOAEL of 3 mg/kg bw per day, haemotoxicity).

Summary
Iprodione
ADI = 0.02 mg/kg bw per day (2-year rabbit)
ARfD = 0.06 mg/kg bw per day (rabbit, developmental)
AOEL = 0.04 mg/kg bw per day (rabbit, developmental)
AAOEL = 0.04 mg/kg bw per day (rabbit, developmental)

3,5-dichloroaniline
ADI = 0.0005 mg/kg bw per day (90-day rat)
ARfD = 0.0075 mg/kg bw per day (28-day rat)

Reference

Peer review of the pesticide risk assessment of the active substance iprodione. European Food Safety Authority. EFSA Journal 2016;14(11):4609. (See Appendix A for substance properties)

3.2.3 Description of ecotoxicological properties of the chemical

Aquatic species

Fish

LC_{50} (mortality) = 3.1 mg/L (*Ictalurus punctatus*, acute 96h flow-through)
LC_{50} (mortality) = 0.550 mg/L (*Lepomis macrochirus*, acute 96h flow-through, test substance RP 30228)
LC_{50} (ELS, 28d) = 1.3 mg/L (*Danio rerio*, chronic, semi-static, test substance RP 32596)
NOEC (Partial LC, 56 d) = 0.0731 mg/L (*Pimephales promelas*, chronic flow-through)

Aquatic invertebrates
EC_{50} (mortality) = 0.660 mg/L (*Daphnia magna*, 48 h static)
EC_{50} (mortality) > 0.500 mg/L (*Daphnia magna*, 48 h static, test substance RP 30228)
EC_{50} (mortality) = 0.364 mg/L (*Daphnia magna*, 48 h static, test substance RP 36221)
EC_{50} (mortality) = 56.28 mg/L (*Daphnia magna*, 48 h static, test substance RP 25040)
EC_{50} (mortality) = 1.26 mg/L (*Daphnia magna*, 48 h static, test substance RP 32596)
NOEC (reproduction) = 0.0075 mg/L (*Americamysis bahia*, 28d flowthrough)
NOEC = 0.057 mg/L (Chironomus riparius, 28d static, test substance RP 30228, spiked water)
NOEC = 95.3 mg/L (Chironomus riparius, 28d static, test substance RP 30228, spiked sediment)

Algae
E_rC_{50} (growth rate) > 1.5 mg/L (Pseudokirchneriella supcapitata, 72h static)
E_rC_{50} (growth rate) > 0.352 mg/L (Scenedesmus subspicatus, 72h static, test substance RP 30228)
E_rC_{50} (growth rate) = 0.567 mg/L (Pseudokirchneriella supcapitata, 72h static, test substance RP 36221)
E_rC_{50} (growth rate) = 86.9 mg/L (Pseudokirchneriella supcapitata, 72h static, test substance RP 25040)
E_rC_{50} (growth rate) = 7.76 mg/L (Pseudokirchneriella supcapitata, 72h static, test substance RP 32596)

Reference

Peer review of the pesticide risk assessment of the active substance iprodione. European Food Safety Authority. EFSA Journal 2016;14(11):4609. (See Appendix A for substance properties)

SECTION 4 DESIGNATED NATIONAL AUTHORITY

Institution	European Commission
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Date, signature of DNA and official seal: 5.11.2019 J. Helbig

EUROPEAN COMMISSION
DG ENVIRONMENT

PLEASE RETURN THE COMPLETED FORM TO:

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Definitions for the purposes of the Rotterdam Convention according to Article 2:

(a) 'Chemical' means a substance whether by itself or in a mixture or preparation and whether manufactured or obtained from nature, but does not include any living organism. It consists of the following categories: pesticide (including severely hazardous pesticide formulations) and industrial;

(b) 'Banned chemical' means a chemical all uses of which within one or more categories have been prohibited by final regulatory action, in order to protect human health or the environment. It includes a chemical that has been refused approval for first-time use or has been withdrawn by industry either from the domestic market or from further consideration in the domestic approval process and where there is clear evidence that such action has been taken in order to protect human health or the environment;

(c) 'Severely restricted chemical' means a chemical virtually all use of which within one or more categories has been prohibited by final regulatory action in order to protect human health or the environment, but for which certain specific uses remain allowed. It includes a chemical that has, for virtually all use, been refused for approval or been withdrawn by industry either from the domestic market or from further consideration in the domestic approval process, and where there is clear evidence that such action has been taken in order to protect human health or the environment;

(d) 'Final regulatory action' means an action taken by a Party, that does not require subsequent regulatory action by that Party, the purpose of which is to ban or severely restrict a chemical.