Committee for Risk Assessment

RAC

Opinion
proposing harmonised classification and labelling at EU level of

azoxystrobin (ISO); methyl (*E*)-2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate

EC Number: -
CAS Number: 131860-33-8

CLH-O-0000001412-86-206/F

Adopted

8 June 2018

8 June 2018

CLH-O-0000001412-86-206/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name:	azoxystrobin (ISO); methyl (*E*)-2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate
EC Number:	-
CAS Number:	131860-33-8

The proposal was submitted by the United Kingdom and received by RAC on 6 July 2017.

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

The United Kingdom has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at *http://echa.europa.eu/harmonised-classification-and-labelling-consultation/* on 13 September 2017. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by 30 October 2017.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC:	Brendan Murray
Co-Rapporteur, appointed by RAC:	Kostas Andreou

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on 8 June 2018 by consensus.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard Statement Code(s)	Pictogram, Signal Word Code(s)	Hazard Statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	607-256-00-8	azoxystrobin (ISO); methyl (2E)-2-(2-{[6-(2-cyanophenoxy)pyrimidin-4-yl]oxy}phenyl)-3-methoxyacrylate		131860-33-8	Acute Tox. 3* Aquatic Acute 1 Aquatic Chronic 1	H331 H400 H410	GHS06 GHS09 Dgr	H331 H410			
Dossier submitters proposal	607-256-00-8	azoxystrobin (ISO); methyl (*E*)-2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate		131860-33-8	Modify Acute Tox. 3 Retain Aquatic Acute 1 Aquatic Chronic 1	Modify H331 Retain H400 H410	Modify GHS06 Retain GHS09 Dgr	Modify H331 Retain H410		Add M=10 M=10 inhalation: ATE=0.7 mg/L (dust or mist)	
RAC opinion	607-256-00-8	azoxystrobin (ISO); methyl (*E*)-2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate		131860-33-8	Acute Tox. 3 Aquatic Acute 1 Aquatic Chronic 1	H331 H400 H410	GHS06 GHS09 Dgr	H331 H410		M=10 M=10 inhalation: ATE=0.7 mg/L (dust or mist)	
Resulting Annex VI entry if agreed by COM	607-256-00-8	azoxystrobin (ISO); methyl (*E*)-2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate		131860-33-8	Acute Tox. 3 Aquatic Acute 1 Aquatic Chronic 1	H331 H400 H410	GHS06 GHS09 Dgr	H331 H410		M=10 M=10 inhalation: ATE=0.7 mg/L (dust or mist)	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

The active substance azoxystrobin is a pesticide (broad-spectrum 'Qo' inhibitor fungicide – see below) and biocide (product-type 7, 9 and 10 - film preservatives; fibre, leather, rubber and polymerised materials preservatives; and construction material preservatives, respectively), which has an existing entry in Annex VI of the Regulation (EC) No 1272/2008 (CLP Regulation) as Acute tox. 3*; H331, Aquatic Acute 1; H400, Aquatic Chronic 1; H410, with no M-factors.

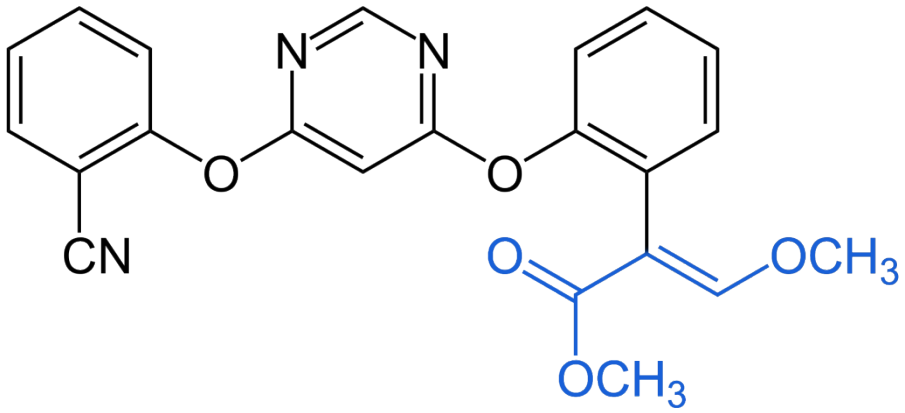

Figure 1: Azoxystrobin: Basic structure, the toxophore is the β-methoxyacrylate portion (shown in blue)

The Qo fungicides inhibit plant pathogens by blocking their ability to produce energy. They do this by blocking the transfer of electrons at the Quinone "outside" site of the bc1 complex (complex III in the electron transport chain).

The DS proposal in the CLH report for human health hazards seeks to update the existing entry by confirming the classification for acute toxicity via the inhalation route (i.e. to remove the minimum classification or "*") and to add the ATE value as well as to re-evaluating the environmental hazard classes. Other hazard classes were not addressed.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Only acute toxicity via the inhalation route was considered in this proposal. The substance was originally classified for human health under the Dangerous Substances Directive (Dir 67/548/EEC or DSD) in the late 1990's as T; R23. This classification was transposed to Acute Tox. 3*; H331 – Toxic if inhaled in Annex VI of the CLP Regulation. The DS proposal seeks to update the existing entry by confirming the classification for acute toxicity via the inhalation route (i.e. to remove the *, i.e. the minimum classification) and to add the ATE value (0.7 mg/L (dust or mist)).

Two studies in rats were presented and summarised (Anon., 1997 and Anon., 1992). Only one was considered sufficient for classification purposes (Anon., 1992) due to the unacceptably high

MMAD (Mass Median Aerodynamic Diameter) values (> 14 µm), observed in the more recent 1997 study (guideline requires an MMAD of 1-4 µm).

In the Anon. (1992) acute inhalation study in rats (Crl:(WI)BR strain; 5/sex/dose), the LC_{50} of azoxystrobin was found to be 0.698 mg/L in females and 0.962 mg/L in males, confirming the existing classification in category 3 and allowing for the removal of the minimal classification (i.e. *) and the addition of an ATE value of 0.7 mg/L (dust or mist).

Comments received during public consultation

Three MSCAs commented in the PC in support of the proposed classification for acute inhalation toxicity. Two supported the proposed ATE of 0.7 mg/L. The third, while supporting the classification, did not agree with proposed ATE stating that with a more conservative approach, a value of 0.5 mg/L, should be adopted. The DS responded that this could be considered by RAC.

Assessment and comparison with the classification criteria

In a 4-hour acute inhalation study, the LC_{50} was determined to be 0.698 mg/L in females and 0.962 mg/L in males. An LC_{50} of > 4.7 mg/L was determined in a second study, but it is noted that the particle size of the test material was relatively high (i.e., the MMAD of the test material was > 14 µm). According to Annex I: 3.1.2.3.2 of CLP, dusts and mists with particle sizes in the range 1 – 4 µm mean mass aerodynamic diameter (MMAD) inhaled by rats are applicable to human exposure. Therefore, it is considered that only the values from the earlier study (1992) should be considered for classification.

It is noted by RAC that the applicant conducted the subsequent (1997) acute inhalation study with a particle size that more accurately represents the particle size of azoxystrobin technical grade active ingredient as manufactured.

In the 1992 study, there were no deaths in animals exposed to 257 µg/L azoxystrobin technical. One male died and one female was killed *in extremis* during exposure to 511 µg/L. One male and one female died and two females were killed *in extremis* during exposure to 767 µg/L azoxystrobin. One male died and two further males were killed *in extremis* during exposure to 1010 µg/L (see table below) but all the females survived.

Darkening and mottling of the lungs were observed in rats that died or were killed prior to the scheduled termination of the study. The LC_{50} for males was calculated at 0.962 mg/L and at 0.698 (0.70) mg/L for females.

For dusts and mists, classification in category 3 is appropriate where 0.5 mg/L < ATE ≤ 1.0 mg/L. Therefore, considering the results in the one acceptable study provided (Anon. 1992), the criteria for classification in category 3 are met and the * should be removed from the existing Annex VI entry.

The proposed ATE of 0.7 mg/L is supported by RAC; it is the lowest LC_{50} estimated from the data and considered sufficiently protective.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

With this proposal, the DS sought to confirm the existing entry for aquatic hazards, namely Aquatic Acute 1 and Aquatic Chronic 1, as well as to introduce M-factors.

Azoxystrobin was considered by the DS as not rapidly degradable for classification purposes with a low bioaccumulation potential. The lowest acute and chronic endpoints were an EC_{50} value of 0.055 mg/L and a NOEC value of 0.00954 mg/L, respectively. These endpoints are both for the aquatic invertebrate *Americamysis bahia* (mysid shrimp). Based on these endpoints the DS proposed an environmental classification as Aquatic Acute 1 (H400) with an M-factor of 10 and Aquatic Chronic 1 (H410) with an M-factor of 10.

Degradation

The results of a hydrolysis study (OECD TG 111) showed that azoxystrobin was stable at pH 4, 7 and 9 at 25°C and at pH 5 and 7 at 50°C. Azoxystrobin was hydrolysed relatively fast at pH 9 at 50°C with a DT_{50} 12.08 days. A second GLP compliant study showed fast hydrolisation of azoxystrobin at pH 9 with a DT50 of 2.6 days (60 ^{o}C). Hydrolysis is not expected to represent a significant pathway for degradation of azoxystrobin under realistic environmental conditions.

Azoxystrobin was shown to photodegrade in a photolysis study (OECD TG 316). It degraded extensively in irradiated samples under 30 days Florida summer sunlight. For azoxystrobin the DT_{50} was calculated to be 8.4 days and during the study more than 15 photo degradants were observed 6 of which being identified.

No ready biodegradability screening tests were conducted on azoxystrobin. The degradation of azoxystrobin was studied in two different natural water-sediment systems (GLP, German BBA Guideline Part IV, Section 5-1). Mineralisation to CO_2 reached 2% to 6% of the applied radioactivity after 152 days. Degradation of azoxystrobin from the whole system was modelled using SFO kinetics: DT_{50} values at 20°C are 234 and 180 days for the Old Basing and Virginia Water systems respectively. At the average EU outdoor temperature of 12°C, DT_{50} values are 444 days and 341 days for the Old Basing and Virginia Water systems respectively. An outdoor mesocosm study was also conducted (GLP, SETAC (1991), Crossland *et al.*, 1992). The calculated water phase $DissT_{50}$ was 13.1 days and the $DissT_{90}$ was 43.6 days. Therefore, the DS concluded that azoxystrobin is considered not rapidly degradable for the purpose of classification and labelling.

Bioaccumulation

No experimental BCF study is available but an estimated fish BCF of 26.61 has been calculated using biocides methodology based on the Log K_{OW}. The experimentally derived Log K_{OW} for azoxystrobin is 2.5, this is less than the trigger value of 4 given in the CLP Regulation. The DS concluded that azoxystrobin has low bioaccumulation potential.

Aquatic Toxicity

The ecotoxicological test results from available acute and chronic studies for all trophic levels of azoxystrobin are summarised in the following table and sections. Only endpoints with technical azoxystrobin were included by the DS.

Table: Summary of the relevant toxicity information on fish, aquatic invertebrates and algae/aquatic plants (the most sensitive data per species are highlighted in bold).

Test organism	Guideline	Exposure	Toxicity (mg/L)
Toxicity to fish			
Oncorhynchus mykiss	OECD TG 203, GLP	96h	LC_{50} - 0.47 (mm)
Lepomis macrochirus	US EPA E 72-1, GLP	96h	LC_{50} - 1.1 (mm)
Cyprinus carpio	OECD TG 203, GLP	96h	LC_{50} - 1.6 (mm)
Cyprinodon variegatus	EPA 72-3, GLP	96h	LC_{50} - 0.66 (mm)
Pimephales promelas	US EPA 72-4, GLP	28d	NOEC - 0.147 (mm)
Oncorhynchus mykiss	OECD TG 204, GLP	28d	NOEC - 0.16 (nom)
Toxicity to aquatic invertebrates			
Daphnia magna	EU method C.2/ OECD TG 202/ EPA-540/9-85-005, GLP	48h	EC_{50} - 0.23 (mm)
Daphnia magna	EU method C.2/ OECD TG 202/ EPA-540/9-85-005, GLP	48h	EC_{50} - 0.28 (mm)
Macrocyclops fuscus	No specific guideline, GLP	48h	EC_{50} - 0.13 (nom)
Americamysis bahia (Mysidopsis bahia)	EPA 72-3, GLP	96h	EC_{50} - 0.055 (nom)
Crassostrea gigas	EPA 72-3, GLP	48h	EC_{50} - 1.3 (nom)
Chironomus riparius	No specific guideline, not a sediment study, GLP	48h	EC_{50} - 0.21 (nom)
Daphnia magna	EPA-540/9-86-141, GLP	21d	NOEC - 0.044 (mm)
Americamysis bahia (Mysidopsis bahia)	US EPA 72-4, GLP	28d	NOEC - 0.00954 (mm)
Chironomus riparius[*]	BBA (1995), GLP	25d	NOEC - 0.8 water (nom)
Chironomus riparius[#]	SETAC-Europe (1993) and ASTM (1993), GLP	33d	NOEC - 23 mg/kg sediment d.w. (mm)
Toxicity to algae and aquatic plants			
Pseudokirchneriella subcapitata (Selenastrum capricornutum)	OECD TG 201, GLP	72h	E_rC_{50} - 1.47 (mm) NOE_rC - 0.038 (mm)
Anabaena flos-aquae	EPA FIFRA 123-2, GLP	72h	E_rC_{50} - 13.9 (mm) NOE_rC - 8.5 (mm)
Navicula pelliculosa	EPA FIFRA 123-2, GLP	72h	E_rC_{50} - 0.146 (nom) NOE_rC - 0.02 (nom)
Skeletonema costatum	EPA FIFRA 123-2, GLP	72h	E_rC_{50} - 0.3 (nom)
Lemna gibba	EPA 123-2, GLP	14d	EC_{50} - 3.2 (nom) NOEC - 0.8 (nom)

mm = endpoint based on mean measured concentrations

nom = endpoint based on nominal concentrations

Acute toxicity

For fish, four studies were available**.** *O. mykiss* was the most sensitive fish species tested in the acute studies, with a 96h LC_{50} of 0.47 mg/L based on mean measured concentrations.

Six studies were available for aquatic invertebrates. *Mysidopsis bahia* was the most sensitive species tested in the acute studies, with a 96h EC_{50} of 0.055 mg/L based on mean measured concentrations.

Four acute toxicity studies were available for algae and aquatic plants. *Navicula pelliculosa* was the most sensitive species with an E_rC_{50} of 0.146 mg/L based on nominal concentrations.

Chronic toxicity

For fish, two flow-through studies were available. *P. promelas* was the most sensitive fish species tested in the chronic studies, with a 28d NOEC 0.147 mg/L based on mean measured concentrations.

Long-term toxicity to aquatic invertebrates was assessed based on four available studies. *Mysidopsis bahia* was the most sensitive species tested in the acute studies, with a 28d NOEC of 0.00954 mg/L based on nominal concentrations.

According to the CLH guidance, a 7 days growth endpoint for *L. gibba* is preferred to a 14 days endpoint, but no 7d toxicity data are available in the CLH report. The 14d NOEC was 0.8 mg/L, based on nominal concentrations.

Comments received during public consultation

Comments were received during the public consultation from 4 MSCAs and 1 Company-Downstream user. All 4 MSCAs were in support of the proposed classification and labelling regarding aquatic hazards (acute and chronic). The Company-Downstream user had an editorial comment on the aqueous photolysis of azoxystrobin as it presented in the CLH report.

Assessment and comparison with the classification criteria

Degradation

Azoxystrobin is considered hydrolytically stable under environmental conditions but undergoes aqueous photolysis to produce a number of photodegradation products. In a laboratory aerobic water-sediment study azoxystrobin was observed to degrade slowly. Whole system degradation DT50 values were estimated to be 341 and 444 days at 12°C. Minimal mineralisation was observed. In an outdoor mesocosm study azoxystrobin was observed to partition into the sediment phase where it slowly dissipated. Based on the available data, azoxystrobin is not degraded (abiotically and/or biotically) in the aquatic environment to a level of > 70% within a 28 day window or transformed to non-classifiable products. Consequently, azoxystrobin is considered not rapidly degradable for the purpose of classification and labelling.

Bioaccumulation

No experimental BCF study is available, azoxystrobin has a Log K_{OW} = 2.5 at 20°C which is below the criterion of $K_{OW} \geq 4$.

Aquatic Toxicity

Acute toxicity

The critical acute results are an LC_{50} of 0.47 mg/L (fish), an EC_{50} of 0.055 mg/L (crustacean), an E_rC_{50} of 0.146 mg/L (algae), and an EC_{50} of 3.2 mg/L (aquatic plants). Therefore, for acute (short-

term) aquatic hazard, azoxystrobin fulfils the criterion of ≤ 1 mg/L. The lowest acute endpoint is the nominal 96h EC_{50} of 0.055 mg/L from the study with *Mysid* shrimp. These values is in the range of 0.01 < $L(E)C_{50}$ ≤ 0.1 mg/L which justifies an acute M-factor of 10.

Chronic toxicity

The critical chronic results are a NOEC of 0.147 mg/L (fish), a NOEC of 0.00954 mg/L (crustacean), a NOE_rC of 0.02 mg/L (algae) and a NOEC of 0.8 mg/L (aquatic plants). The lowest chronic endpoint is the 28 day mean measured NOEC of 0.00954 mg/L from the study with *Mysid* shrimp. This value is below 0.01 mg/L which is the classification threshold for Aquatic Chronic 1 for not rapidly degradable substances, and justifies a chronic M-factor of 10 (0.001 < NOEC ≤ 0.01 mg/L).

There are no acute data available for *P. promelas* and thus any extrapolation for chronic toxicity for other fish species based on the acute:chronic ratio was not possible. However, if this assessment had been performed is unlikely to alter the classification as proposed below.

Conclusion on classification

Azoxystrobin is considered not rapidly biodegradable and has low potential of bioaccumulation. In agreement with the DS, RAC is of the opinion that azoxystrobin should be classified as:

Aquatic Acute 1 – H400 'Very toxic to aquatic life' with an M factor = 10, and Aquatic Chronic 1 - H410 'Very toxic to aquatic life with long lasting effects' with M factor= 10.

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).