Peer review of the pesticide risk assessment of the active substance bromoxynil (variant evaluated bromoxynil octanoate)

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Abstract

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

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Keywords: bromoxynil, peer review, risk assessment, pesticide, herbicide

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Erratum: Appendix A has been republished to correct errors in the original version. The changes relate to amendments made to footnotes on p. 21 and 22, removal of a footnote on p. 13, and renumbering of subsequent footnotes. In addition, an amendment was made to the peer review proposal for harmonised classification for bromoxynil butyrate on page 22.

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Summary

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

In accordance with Article 1 of the Regulation, the rapporteur Member State (RMS), France, and co-rapporteur Member State (co-RMS), Germany, received an application from Bayer CropScience on behalf of the Bromoxynil Task Force (Bayer CropScience and Nufarm UK Limited) for the renewal of approval of the active substance bromoxynil. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicants, the co-RMS, the European Commission and the European Food Safety Authority (EFSA) about the admissibility.

The RMS provided its initial evaluation of the dossier on bromoxynil in the renewal assessment report (RAR), which was received by EFSA on 21 March 2016. In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicants, Bayer CropScience on behalf of the Bromoxynil Task Force (Bayer CropScience and Nufarm UK Limited), for comments on 1 June 2016. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 2 August 2016.

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

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

The conclusions laid down in this report were reached on the basis of the evaluation of the representative uses of bromoxynil as a herbicide on maize and straw cereals, as proposed by the applicants. Full details of the representative uses can be found in Appendix A of this report.

The use of bromoxynil according to the representative uses proposed at the European Union (EU) level results in a sufficient herbicidal efficacy against the target weeds.

In the section identity, physical chemical properties, analytical methods, a data gap was identified for additional validation data for the confirmatory method for the method for residues in animal matrices. Pending on the final residue definition for monitoring for animal matrices additional validation data might be required.

In the area of mammalian toxicology and non-dietary exposure, further data are needed to assess the endocrine potential of bromoxynil and its esters. The peer review proposal of classification of bromoxynil and its esters in category 1B for reproductive toxicity lead to a critical area of concern. In addition, the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine disrupting properties may be met.

In the residue section, a data gap was identified for the metabolism studies on cereals compliant with the representative good agricultural practices (GAP). The consumer risk assessment could not be finalised for the products of animal origin considering the outstanding data to perform a comprehensive livestock exposure assessment. A data gap for the determination of the residues in pollen and bee products for human consumption resulting from residues taken up by honeybees from crops at blossom was identified.

The data available on environmental fate and behaviour are sufficient to carry out the required environmental exposure assessments at the EU level for the representative uses. Considering that the representative formulation is ‘Bromoxynil-octanoate EC 327.5 G’, containing as active substance bromoxynil octanoate only, the present conclusion refers to octanoate ester of bromoxynil and its metabolites. Further studies may be necessary for the risk assessment of esters of bromoxynil other than the octanoate. A data gap was identified for information on the effect of water treatment processes on the nature of residues of metabolites potentially present in surface water, when surface water is abstracted for drinking water. This gap leads to the consumer risk assessment from the consumption of drinking water being not finalised for all the representative uses.

In the area of ecotoxicology, a critical area of concern for high long-term risk assessment for wild mammals has been identified. The risk assessment to aquatic plants exposed to bromoxynil octanoate could not be finalised due to the lack of suitable data. Several data gaps have also been identified.
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Background

Commission Implementing Regulation (EU) No 844/2012¹ (hereinafter referred to as ‘the Regulation’) lays down the provisions for the procedure of the renewal of the approval of active substances, submitted under Article 14 of Regulation (EC) No 1107/2009². This regulates for the European Food Safety Authority (EFSA) the procedure for organising the consultation of Member States, the applicants and the public on the initial evaluation provided by the rapporteur Member State (RMS) and/or co-rapporteur Member State (co-RMS) in the renewal assessment report (RAR), and the organisation of an expert consultation where appropriate.

In accordance with Article 13 of the Regulation, unless formally informed by the European Commission that a conclusion is not necessary, EFSA is required to adopt a conclusion on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 within 5 months from the end of the period provided for the submission of written comments, subject to an extension of up to 8 months where additional information is required to be submitted by the applicants in accordance with Article 13(3).

In accordance with Article 1 of the Regulation, the RMS France and co-RMS Germany received an application from Bayer CropScience on behalf of the Bromoxynil Task Force (Bayer CropScience and Nufarm UK Limited) for the renewal of approval of the active substance bromoxynil. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicants, the co-RMS (Germany), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on bromoxynil in the RAR, which was received by EFSA on 21 March 2016 (France, 2016).

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicants, Bayer CropScience on behalf of the Bromoxynil Task Force (Bayer CropScience and Nufarm UK Limited), for consultation and comments on 1 June 2016. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 2 August 2016. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicants were invited to respond to the comments in column 3 of the reporting table. The comments and the applicants’ response were evaluated by the RMS in column 3.

The need for expert consultation and the necessity for additional information to be submitted by the applicants in accordance with Article 13(3) of the Regulation were considered in a telephone conference between EFSA and the RMS on 13 October 2016. On the basis of the comments received, the applicants’ response to the comments and the RMS’s evaluation thereof, it was concluded that additional information should be requested from the applicants, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues and ecotoxicology.

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

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

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

This conclusion report summarises the outcome of the peer review of the risk assessment of the active substance and the representative formulation, evaluated on the basis of the representative uses of bromoxynil as a herbicide on maize and straw cereals, as proposed by the applicants. A list of the relevant end points for the active substance and the formulation is provided in Appendix A.

¹ Commission Implementing Regulation (EU) No 844/2012 of 18 September 2012 setting out the provisions necessary for the implementation of the renewal procedure for active substances, as provided for in Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. OJ L 252, 19.9.2012, p. 26–32.
² Regulation (EC) No 1107/2009 of 21 October 2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p. 1–50.
In addition, a key supporting document to this conclusion is the peer review report (EFSA, 2017), which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the initial commenting phase to the conclusion. The peer review report comprises the following documents, in which all views expressed during the course of the peer review, including minority views, where applicable, can be found:

- the comments received on the RAR;
- the reporting table (17 October 2016);
- the evaluation table (6 April 2017);
- the reports of the scientific consultation with Member State experts (where relevant);
- the comments received on the assessment of the additional information (where relevant);
- the comments received on the draft EFSA conclusion.

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

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

The active substance and the formulated product

Bromoxynil is the ISO common name for 3,5-dibromo-4-hydroxybenzonitrile (IUPAC). The esters of bromoxynil are derivatives of this active substance. Bromoxynil butyrate, bromoxynil heptanoate and bromoxynil octanoate are the modified ISO common names for 2,6-dibromo-4-cyanophenyl butyrate, 2,6-dibromo-4-cyanophenyl heptanoate and 2,6-dibromo-4-cyanophenyl octanoate (IUPAC), respectively.

The representative formulated product for the evaluation was ‘Bromoxynil-octanoate EC 327.5 G’, an emulsifiable concentrate (EC) containing 327.5 g/L bromoxynil octanoate (equivalent to 225 g/L pure bromoxynil).

The representative uses evaluated were spray applications in maize, spring barley, spring wheat and oats, and in winter wheat, winter barley, rye and triticale to control dicotyledonous weeds. Full details of the Good Agricultural Practices (GAPs) can be found in the list of end points in Appendix A.

Data were submitted to conclude that the use of bromoxynil octanoate according to the representative uses proposed at the EU level results in a sufficient herbicidal efficacy against the target weeds following the guidance document SANCO/2012/11251-rev. 4 (European Commission, 2014b).

The literature search dealing with side effects on health, the environment and non-target species was conducted and considered appropriate for all sections.

Conclusions of the evaluation

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

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

Bromoxynil is produced as a technical concentrate (TK), a wet cake, containing up to 10% of water. The proposed specification is based on batch data from industrial scale production and on quality control (QC) data. The minimum purity of the technical material is 970 g/kg on dry weight basis. There is no FAO specification available for bromoxynil.

Bromoxynil is only produced to be used in the synthesis of the esters. The proposed specification for bromoxynil butyrate is based on batch data from industrial scale production. The minimum purity of the technical material is 967 g/kg. There is no FAO specification available for bromoxynil butyrate.

The proposed specification for bromoxynil octanoate is based on batch data from industrial scale production and QC data. The minimum purity of the technical material is 945 g/kg. The minimum purity is meeting the requirements of the FAO specification available for bromoxynil octanoate (AGP:CP/340, Rome, 1996) of not less than 920 g/kg bromoxynil octanoate, developed under the old procedure.

The proposed specification for technical material of the octanoate/heptanoate mixed esters of bromoxynil is based on batch data from industrial scale production and QC data. The proposed minimum purities are 480 g/kg bromoxynil octanoate and 460 g/kg bromoxynil heptanoate, respectively. It should
be noted that a FAO specification is available for bromoxynil heptanoate (AGP:CP/339, Rome, 1996) with a bromoxynil heptanoate content not less than 930 g/kg, developed under the old procedure.

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

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

The residue definition for monitoring for plant, animal and environmental matrices was set to bromoxynil and its esters, expressed as bromoxynil. Monitoring the compounds of the residue definition in food and feed of plant origin can be done by high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) method with a limit of quantification (LOQ) of 0.01 mg/kg, expressed as bromoxynil, in all commodity groups. A gas chromatography with electron capture detector (GC-ECD) method is available for the determination of residues of bromoxynil and its esters in food of animal origin with a LOQ of 0.01 mg/kg in milk and 0.05 mg/kg in meat, liver, kidney, fat and egg, expressed as bromoxynil. A data gap was however identified for additional validation data for the confirmatory method for the method for residues in animal matrices. Pending on the final residue definition for monitoring for animal matrices additional validation data might be required.

Liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods are available enabling the determination of residues of bromoxynil and its esters in the environmental matrices with LOQs of 0.01 mg/kg in soil, 0.05 μg/L in surface water and 0.2 μg/m³ in the air, respectively, all expressed as bromoxynil.

Bromoxynil residues in body fluids can be monitored by gas chromatography–mass spectrometry (GC-MS) with a LOQ of 0.05 mg/L, while for the analysis of body tissues the monitoring method of residues in foodstuffs of animal origin can be used.

2. Mammalian toxicity

The toxicological profile of the active substance bromoxynil and its esters was discussed at the Pesticides Peer Review Experts’ Meeting 151 and assessed based on the following guidance documents: SANCO/221/2000-rev. 10-final (European Commission, 2003), SANCO/10597/2003-rev. 10.1 (European Commission, 2012), Guidance on Dermal Absorption (EFSA PPR Panel, 2012) and Guidance on the Application of the CLP Criteria (ECHA, 2015).

To assess the toxicological profile of the active substance bromoxynil and its esters, the applicants submitted a set of valid toxicity studies. The toxicity studies supported the proposed technical specification for the active substance and associated impurities. Impurities are considered non-relevant from the toxicological point of view. The different esters are considered toxicologically equivalent unless indicated otherwise.

The pesticide mode of action of bromoxynil, i.e. uncoupling of oxidative phosphorylation, might lead to liver toxicity and to increased metabolic rate producing excessive heat and hyperthermia in mammals.

In the toxicokinetics studies, bromoxynil was extensively absorbed. Oral absorption was estimated to be greater than 80%. There was no evidence for accumulation. Excretion of bromoxynil was predominantly through the urine. The main metabolic pathway identified was hydrolysis and conjugation. No unique human metabolite is expected.

In the acute toxicity studies, bromoxynil and its esters have moderate to very high acute toxicity when administered orally or by inhalation and have low acute toxicity when administered dermally to rats. Bromoxynil and most of its esters are not skin or eye irritants but they are skin sensitisers. Bromoxynil is not phototoxic.

In short-term oral toxicity studies with rats, mice and dogs, the target organ was the liver. Critical effects in dogs also included clinical signs (panting) and reduced body weight. In Fischer F344 rats, an additional critical effect was thyroid toxicity. The dog was the most sensitive species. The relevant short-term oral no observed adverse effect level (NOAEL) is 0.3 mg/kg body weight (bw) per day (90-day and 1-year dog studies).

Based on available genotoxicity studies, the substance is unlikely to be genotoxic.

In long-term toxicity and carcinogenicity studies with rats and mice, the critical effects included liver toxicity in rats and mice. The mouse was the most sensitive species. Bromoxynil showed carcinogenic
potential in mice (hepatocellular adenoma and carcinoma). The weight of evidence analysis of the available data (new mechanistic studies and studies from the dossier) suggests that Peroxisome proliferator-activated receptor alpha (PPARα) induction by bromoxynil is the underlying mode of action of liver tumours observed in mice. This mode of action is not relevant for humans according to CLP criteria (ECHA, 2015).

In reproductive toxicity studies, fertility and overall reproductive performance was not impaired; the parental and offspring NOAELs are 3.39 mg/kg bw per day, whereas the reproductive NOAEL is 17.75 mg/kg bw per day. In the developmental toxicity studies in rats and rabbits, there was evidence of teratogenicity in both species. Bromoxynil and its esters (octanoate and heptanoate) are currently listed in Annex VI of the CLP Regulation (EC) No 1272/2008 as Repr. 2 H361d: Suspected of damaging the unborn child. The developmental toxicity studies were available in the original dossier, but EFSA does not have information regarding the assessment of developmental toxicity effects by the European Chemicals Bureau regarding the consideration of the substance under the previous regulatory frame for classification and labelling. The RMS assessed the original developmental toxicity studies according to current criteria for defining malformations versus variations and the CLP criteria (ECHA, 2015). The RMS proposed a revised classification and labelling as Repr. 1B H360D: May damage the unborn child instead of Repr. 2 H361d. The experts supported the revision of the classification. The classification and labelling of bromoxynil as Repr. 1B is proposed and a critical area of concern is identified with regard to the approval criteria, Annex II, Point 3.6.4 of Regulation (EC) No 1107/2009.

No potential for neurotoxicity was observed in the standard toxicity studies and in the acute neurotoxicity study in rats. Bromoxynil and its esters are currently classified as toxic for reproduction category 2, in accordance with the provisions of Regulation (EC) No 1272/2008, and toxic effects on the endocrine organs have been observed in the available data (i.e. thyroid toxicity in Fischer F344 rats and uterus in rats); therefore, the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine disrupting properties may be met leading to a critical area of concern. With regard to the scientific risk assessment, the experts agreed that thyroid toxicity in Fischer F344 rats might be endocrine mediated. Mechanistic information from the public domain also indicated potential mode of action of thyroid toxicity of bromoxynil. No evidence of thyroid toxicity in other studies/species and in other rat strains was observed. The experts proposed a data gap for further investigations of the potential endocrine-mediated properties of bromoxynil concerning thyroid toxicity.

The reassessment of the toxicological profile of bromoxynil and its esters leads to a revision of the existing toxicological reference values (European Commission, 2004). The agreed acceptable daily intake (ADI) and systemic acceptable operator exposure level (AOEL) are 0.003 mg/kg bw per day (expressed as bromoxynil), on the basis of the relevant short-term NOAEL of 0.3 mg/kg bw in the 90-day and 1-year study in dogs based on increased liver weight, reduced body weight and clinical signs at 1 mg/kg bw per day. An uncertainty factor (UF) of 100 was applied. No correction for oral absorption is needed to derive the AOEL.

The agreed acute reference dose (ARfD) and systemic acute acceptable operator exposure level (AAOEL) are 0.013 mg/kg bw (expressed as bromoxynil) based on the NOAEL of 4 mg/kg bw per day for developmental toxicity effects observed at 12.5 mg/kg bw per day in the developmental toxicity study in rats. An UF of 3 due to severity of developmental effects in addition to the standard uncertainty factor of 100 was applied. The ARfD and AAOEL provide at least a margin of exposure of approximately 1,000 relative to the lowest observable adverse effect level (LOAEL) for malformations in rats and rabbits. No correction for oral absorption is needed to derive the AAOEL.

The RMS estimated non-dietary exposure (i.e. operator, worker, bystander and resident) considering dermal absorption values of bromoxynil in ‘Bromoxynil-octanoate EC 327.5 G’ of 3% for the concentrate (327.5 g/L) and of 14% and 21% for the dilutions (1.23 g/L and 0.82 g/L; respectively) as input values.

The RMS assessed the representative use with ‘Bromoxynil-octanoate EC 327.5 G’ as a herbicide in cereals. The operator exposure was below the AOEL (72% of the AOEL) with the use of personal

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

4 It should be noted that harmonised classification and labelling is formally proposed and decided in accordance with Regulation (EC) No 1272/2008.
3. Residues

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

Bromoxynil was discussed at the Pesticide Peer Review Expert Meeting 153 in February 2017.

The metabolism of bromoxynil in primary crops was investigated in wheat at BBCH (growth stages of mono- and dicotyledonous plants) 13-14 (1.2N) and BBCH 12, in sweet corn at BBCH 10-19 (0.7N), in alfalfa at BBCH 0-13 and in cotton (leaves), upon foliar applications, leaf brushing and stem injection by using 14C-cyano and/or 14C-phenyl radiolabelled bromoxynil esters. The metabolism of bromoxynil esters was depicted in wheat immature green plant, in sweet corn forage and fodder and in alfalfa forage and hay. The old wheat metabolism studies from the 1970s showed that bromoxynil and bromoxynil octanoate were the major compounds of the total residues in immature wheat green plants (up to 18% and 35% of total radioactive residues (TRR), respectively). In the wheat metabolism study submitted under the renewal process, the 2,6-dibromohydroquinone glucoside metabolite was found to be the major component of the total residues in green plant (12% TRR; 0.18 mg eq/kg) while bromoxynil was recovered at a lower proportion (5.5% TRR; 0.08 mg eq/kg) at a 28-day preharvest interval (PHI). In sweet corn, bromoxynil and bromoxynil octanoate were recovered in fodder at significant proportions (37.5% and 10% TRR, respectively) while numerous minor metabolites were identified at a level < 10% TRR (0.03–0.08 mg eq/kg). In forage at 9 days after the treatment, the concentration of these metabolites was found to be significant (0.1–0.52 mg eq/kg). For grains, based on the overall metabolism data, negligible translocation of residues was observed, thus it can be reasonably assumed that the TRRs in cereal grains will be very low. In alfalfa, bromoxynil (free and conjugated) was recovered as the major compound of the total residues in forage and hay (38% and 15% TRR, respectively) along with metabolites detected at a level < 10% TRR, but in significant concentrations (i.e. 14.9 mg eq/kg for M01, 4.01 mg eq/kg for M02 and 2.86 mg eq/kg for M06).

It is noted that the experimental designs of the metabolism studies in wheat and maize were not compliant with the representative uses in terms of dose, mode and growth stage of application (BBCH 13-14 vs BBCH 32). Furthermore, considering the different metabolic patterns of bromoxynil esters depicted, respectively, in wheat, maize and alfalfa, and in the absence of metabolites’ identification in wheat straw at harvest, the experts of the meeting were unable to confidently conclude on the metabolic pathway of bromoxynil. The majority of the experts agreed to request a new wheat metabolism study compliant with the representative use on cereals (data gap). It is, however, highlighted that a minority of experts were of the opinion that a new wheat metabolism study is not necessary as it is postulated that the residues in straw will be constituted of numerous metabolites occurring at low levels considering the growth dilution up to harvest.

However, based on the overall metabolism data, a default residue definition for monitoring and risk assessment as bromoxynil and its esters, expressed as bromoxynil was proposed on cereal grains. For feed items, the residue definition for risk assessment is provisionally set as bromoxynil and its esters, expressed as bromoxynil. This residue definition will need to be reconsidered pending the outcome of the requested wheat metabolism study.

With regard to the persistence of bromoxynil and its esters into the soil, a rapid degradation is observed since the period required for 90% dissipation (DT₉₀) < 30 days, therefore, no further investigation on succeeding crops is needed.

A sufficient number of residue trials compliant with the critical good agricultural practice (cGAP) on maize, barley and wheat are available, and the MRL at the LOQ of 0.01* mg/kg can be derived for

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5 The use of EUROPOEM II was considered a worst case estimate for the inspection activity in treated cereals.
cereal grains (wheat, barley, rye and oats) and maize. Storage stability was investigated with bromoxynil ester analysed as bromoxynil showing the stability of bromoxynil for 12 months when stored at −23°C in high water (onion, forage, alfalfa and grass), high starch (cereal grains) and high oil content (cotton and flax seeds).

Hydrolysis studies considering the nature of residues in processed commodities are not triggered (residue levels in cereal grains < 0.01 mg/kg).

The metabolism in livestock (laying hens and lactating goats) was investigated with bromoxynil octanate and the major component of the total residues was bromoxynil accounting from (80–100%) in all animal matrices. Meanwhile, the residue definitions for monitoring and risk assessment in products of animal origin was provisionally proposed as ‘bromoxynil and its esters, expressed as bromoxynil’ pending the full assessment of the requested wheat metabolism study. Feeding studies were not triggered since the calculated dietary burden for all livestock groups were below 0.004 mg/kg bw per day. However, it should be noted that the agreed residue definition for risk assessment in feed items is provisional; therefore, the livestock dietary burden calculation and the need for additional metabolism and feeding studies might be reconsidered. Fish metabolism studies are not triggered considering the residue levels in cereal grains (< 0.01 mg/kg).

The consumer dietary intake calculation was conducted using from the EFSA Pesticide Residue Intake Model (PRIMO) rev.2 model for acute and chronic dietary risk assessments considering the risk assessment residue definition as bromoxynil and its esters for cereal grain. Long-term or short-term intake concerns were not identified for the consumers since the highest chronic and highest acute intakes accounted for 3.8% of the ADI (WHO Cluster diet B) and 1.1% of the ARfD (for wheat). The consumer risk assessment is not finalised for animal products considering the outstanding data to perform a comprehensive livestock exposure assessment.

It is noted that in the framework of the peer review for the renewal of the approval of bromoxynil, the toxicological reference values were lowered (see Section 2). Furthermore considering that the livestock exposure assessment cannot be finalised, the established MRL under Art 12 of the Regulation (EC) No 396/2005 and the overall consumer exposure assessment might need to be revised (EFSA, 2012).

The data requirement for the determination of the residues in pollen and bee products for human consumption resulting from residues taken up by honeybees from crops at blossom was not addressed; in addition sweet corn metabolism studies showed the systemic behaviour of residues through the plant (data gap).

4. Environmental fate and behaviour

The representative formulation is ‘Bromoxynil-octanoate EC 327.5 G’, containing only bromoxynil octanoate as active substance; therefore, the present evaluation and risk assessment refer to bromoxynil octanoate and its metabolites, for which detailed information was submitted. Endpoints were also provided for bromoxynil heptanoate and for bromoxynil butyrate and have been included in the list of endpoints, but have not been used to carry out the exposure and risk assessment. Further studies may be necessary for the risk assessment of esters of bromoxynil other than the octanoate. However, all laboratory degradation endpoints available for bromoxynil octanoate, bromoxynil heptanoate and bromoxynil butyrate have been pooled to derive an overall geometric mean used for modelling. This approach was accepted in this particular case due to the similar modelling endpoints, the low persistence of the esters in the environmental compartments and their very low mobility in soil. RMS does not agree that further studies may be necessary for the risk assessment of other esters of bromoxynil as bridging from other esters could be sufficient.

The rates of dissipation and degradation in the environmental matrices investigated were estimated using FOCUS (2006) kinetics guidance. In soil laboratory incubations under aerobic conditions in the dark, bromoxynil octanoate exhibited very low to low persistence, forming the major (> 10% applied radioactivity (AR)) metabolites bromoxynil (max. 44.6% AR, when bromoxynil octanoate is applied), 3,5-dibromo-4-hydroxybenzamide (M01, max. 32.4% AR, when bromoxynil octanoate is applied), and 3,5-dibromo-4-hydroxybenzoic acid (M02, max. 34.8% AR, when bromoxynil is applied), which exhibited all very low to low persistence. Mineralisation of the phenyl ring 14C radiolabel to carbon dioxide accounted for 64.3% AR after 90 days when bromoxynil octanoate is applied, and for 33.6% AR after 28 days when bromoxynil is applied. The formation of unextractable residues (not extracted by acetonitrile/water) for this radiolabel accounted for 75.2% AR after 7 days, when bromoxynil octanoate is applied, and for 72.3% AR after 28 days, when bromoxynil is applied. Degradation under anaerobic conditions and photodegradation are not considered significant route of degradation.
Bromoxynil octanoate exhibited immobility in soil and no pH dependence was identified. Bromoxynil and metabolite M02 exhibited high to medium soil mobility, and metabolite M01 exhibited very high to medium soil mobility. It was concluded that the adsorption of all metabolites was pH dependent. In soil column leaching studies, the amount of radioactivity in the leachates when bromoxynil octanoate or bromoxynil was freshly applied ranged from < 1% to 56% AR. The amount of applied radioactivity leached from aged soil columns ranged from < 1% to 57% AR in the leachate. In both types of studies (aged and non-aged), the majority of radioactivity in the leachates was dissolved carbon dioxide; however bromoxynil and 3-bromo-4-hydroxybenzonitrile were detected from a sand soil column.

In laboratory incubations in dark aerobic natural sediment water systems, bromoxynil octanoate exhibited very low persistence, forming the major metabolites bromoxynil (max. 80.4% AR in water, when bromoxynil octanoate is applied), 3-bromo-4-hydroxy-benzonitrile (M03, max. 11.5% AR in water when bromoxynil octanoate is applied), 4-hydroxybenzonitrile (M06, max. 25.4% AR in water when bromoxynil octanoate is applied) and 3,5 dibromo-4-hydroxybenzamide (M01, max. 23.3% AR in water when bromoxynil is applied). The unextractable sediment fraction (not extracted by acetonitrile/water) for the phenyl ring 14C radiolabel accounted for 10.9–18.8% AR at study end (100 days) when bromoxynil octanoate is applied and for 24.9–19% AR at study end (60 days) when bromoxynil is applied. Mineralisation was the major sink for this radiolabel accounting for 55.4–57.2% AR at the end of the study (100 days) when bromoxynil octanoate is applied and for 61.2–65.0% AR at the end of the study (60 days) when bromoxynil is applied.

The rate of decline of bromoxynil octanoate in a laboratory sterile aqueous photolysis experiment was fast; photolysis may be a significant route of degradation under natural aquatic environments. The major photodegradation products when bromoxynil octanoate was applied were 4-hydroxybenzonitrile (M06, max. 10.3% AR) and 2-bromo-4-cyanophenyl octanoate (M09, max. 14% AR). The major photodegradation products when bromoxynil was applied were 3,4-dihydroxybenzonitrile (M13, max. 14.8% AR) and 3-bromo-4,5-dihydroxybenzonitrile (M12, max. 11.4% AR).

The necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC) calculations) were carried out for bromoxynil octanoate and the metabolites bromoxynil, 3,5-dibromo-4-hydroxybenzamide, 3,5-dibromo-4-hydroxybenzoic acid, 3-bromo-4-hydroxybenzonitrile, 4-hydroxybenzonitrile, 3-bromo-4,5-dihydroxybenzonitrile, 3,4-dihydroxy benzonitrile, 2-bromo-4-cyanophenyl octanoate, using the FOCUS (2001) step 1 and step 2 approach (version 3.2 of the Steps 1-2 in FOCUS calculator).

For bromoxynil octanoate and the metabolite bromoxynil, appropriate step 3 (FOCUS, 2001) and step 4 calculations were available. The step 4 calculations appropriately followed the FOCUS (2007) guidance, with no-spray drift buffer zones of up to 25 m being implemented for the drainage scenarios (representing a 91–93% spray drift reduction) for maize, spring cereals and winter cereals (spring application), and combined no-spray buffer zones with vegetative buffer strips of up to 10 m (reducing solute flux in run-off by 80% and erosion run-off of mass adsorbed to soil by 95%) being implemented for the run-off scenarios for winter cereals (autumn application).

The SWAN tool (version 4.0.1) was appropriately used to implement these mitigation measures in the simulations. However, risk managers and others may wish to note that while run-off mitigation is included in the step 4 calculations available, the FOCUS (2007) report acknowledges that for substances with $K_{Foc} < 2,000$ mL/g (i.e. bromoxynil), the general applicability and effectiveness of run-off mitigation measures had been less clearly demonstrated in the available scientific literature, than for more strongly adsorbed compounds.

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (European Commission, 2014a) scenarios and the models PEARL 4.4.4 and PELMO 5.5.3 for bromoxynil octanoate and its metabolites bromoxynil, 3,5-dibromo-4-hydroxybenzamide and 3,5-dibromo-4-hydroxybenzoic acid. For bromoxynil, 3,5-dibromo-4-hydroxybenzamide and 3,5-dibromo-4-hydroxybenzoic acid calculations were carried out taking into account the pH-dependency of adsorption performing simulations using the lowest $K_{Foc}$ values for 3,5-dibromo-4-hydroxybenzamide and 3,5-dibromo-4-hydroxybenzoic acid and the geometric mean $K_{Foc}$ from alkaline soils for bromoxynil. The potential for groundwater exposure from all representative uses by bromoxynil octanoate and its metabolites bromoxynil, 3,5-dibromo-4-hydroxybenzamide and 3,5-dibromo-4-hydroxybenzoic acid above the parametric drinking water limit of 0.1 µg/L was concluded to be low in geoclimatic situations that are represented by all nine FOCUS groundwater scenarios.

The PEC in soil, surface water, sediment and groundwater covering the representative uses assessed can be found in Appendix A of this conclusion.
The applicant did not provide appropriate information to address the effect of water treatments processes on the nature of the residues that might be present in surface water, when surface water is abstracted for drinking water. This has led to the identification of a data gap (see Section 7) and results in the consumer risk assessment not being finalised (see Section 9).

5. Ecotoxicology

The risk assessment was based on the following documents: European Commission (2002a,b), SETAC (2001), EFSA (2009) and EFSA PPR Panel (2013).

The risk assessment for non-target organisms was carried out both for the ester bromoxynil octanoate and bromoxynil. Toxicity studies were also available for bromoxynil heptanoate and for bromoxynil butyrate esters and were included in the list of endpoints, but were not used to carry out a risk assessment.

Several aspects of the risk assessment were discussed at the Peer Review Experts’ meeting 154 in February 2017. For the majority of the chronic toxicity studies only the no observed effect concentration (NOEC) was available. However, according to Commission Regulations (EU) No 283/2013 and 284/2013, for those studies with a study design allowing calculation of EC10 and EC20, these values should be also calculated (data gap).

At the Peer Review Experts’ meeting 154, it was discussed and agreed that for the risk assessment of birds and mammals the exposure to bromoxynil should be calculated considering the molecular ratio and the formation fraction. Considering the limited number of residue trials where the formation fraction of bromoxynil was measured, the experts agreed to use the maximum measured formation fraction.

Based on the available data and Tier 1 risk assessment, low acute risk to birds was identified for both bromoxynil octanoate and bromoxynil for all the representative uses. However, at Tier 1, high long-term risk was identified to large herbivorous birds when exposed to bromoxynil octanoate for the representative use on cereals and for medium herbivorous birds exposed to bromoxynil octanoate or bromoxynil for the representative use on maize.

The available refinement based on the use of a DT50 calculated using all the available residue trials on maize and cereals was discussed and agreed at the Peer Review experts’ meeting 154. The risk to birds was identified as low for all the representative uses.

Based on the available data risk assessment, a high acute risk to small herbivorous mammals exposed to both bromoxynil octanoate and bromoxynil was identified for the representative use on maize. The experts at the Peer Review experts’ meeting 154 agreed to use the rabbit as focal species based on the results from ‘live trapping’ from three field studies for the representative use on maize. Furthermore, the experts agreed that default residue per unit dose (RUD) value can be replaced by refined RUD calculated from residue trials for maize. The experts also agreed using the cereals early shoots scenario as surrogate for the estimation of the food intake rate and the diet composition (food intake rate (FIR)/bw) of rabbit. By using those refinements, a low acute risk to mammals was identified for the representative use on maize.

The long-term endpoint for mammals was discussed at the Peer Review experts’ meeting 154. At Tier 1, a high long-term risk to mammals was identified for large herbivorous mammals and small omnivorous mammals for the representative use on cereals and for small herbivorous and omnivorous mammals for the representative use on maize.

The risk to large herbivorous mammals was refined by using the DT50 derived from residue trials on cereals; however, a high risk was still identified for the representative use on cereals (data gap). For the representative use on maize, the risk to small herbivorous mammals was refined, as explained above. Low risk to small herbivorous mammals was identified. However, no refinements were available for small omnivorous mammals for all the representative uses (data gap).

The risk assessment for birds and mammals exposed to pertinent metabolites formed in plants could not be assessed due to the lack of a suitable metabolism study on cereals (see Section 3) (data gap).

Low risk to birds and mammals was identified from consumption of contaminated water.

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6 Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, 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. OJ L 93, 3-4.2013, p. 1-84 and Commission Regulation (EU) No 284/2013 of 1 March 2013 setting out the data requirements for plant protection products, 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. OJ L 93, 3-4.2013, p. 85-152.
A high risk from secondary poisoning was identified (earthworm-eating birds and mammals) for bromoxynil octanoate. However, considering that bromoxynil octanoate is rapidly degraded into bromoxynil in the environment, overall, the risk of secondary poisoning can be considered low.

Toxicity studies for both bromoxynil octanoate and bromoxynil and for the representative formulation were available on fish and invertebrates including sediment-dwelling organisms. For algae, the only valid studies were conducted with bromoxynil and the formulation. For aquatic plants, only one valid study with *Lemma* sp. and bromoxynil was available. Therefore, a data gap has been identified to address the risk to algae and aquatic plants when exposed to bromoxynil octanoate.

Fish acute toxicity studies and one toxicity study with rooted macrophytes conducted in the presence of sediments for bromoxynil octanoate were available and were discussed at the Peer Review experts’ meeting 154. The experts agreed using a lethal concentration (LC50) expressed as initial measured concentration for the acute toxicity studies with fish. The study with rooted macrophytes was invalidated. In addition, the experts agreed considering those studies as higher tier and therefore the exposure in the studies was compared with the predicted FOCUS exposure profiles. For some scenarios for the representative uses on spring and winter cereals (D1, D2 and D6 for winter cereals and D1 for spring cereals), however, the exposure in the studies was not worst-case, and therefore, the endpoint was not used for the risk assessment.

Overall, for bromoxynil octanoate and all the representative uses, a low risk to fish was identified by using FOCUS step 3 & 4 PECsw with the application of mitigation measures up to 15 m no-spray buffer zone. For invertebrates, a low risk was identified by using FOCUS step 4 PECsw with mitigation measures up to 25 m no-spray buffer zone. For algae, when using the endpoint for the formulation, a low risk was identified using FOCUS step 3 & 4 PECsw by applying mitigation measures up to 5 m no-spray buffer zone.

For bromoxynil, a low risk to fish, invertebrates and algae was identified by using FOCUS step 1 & 2 PECsw for all the representative uses; for plants, a low risk was identified using FOCUS step 1 & 2 PECsw for the representative uses on maize and spring cereals. For the representative use on winter cereals, a low risk to plants was identified by using FOCUS step 3 & 4 PECsw with the application of mitigation measures comparable to 5 m no-spray buffer zone and 10 m vegetative buffer strip.

Overall, low risk to all the pertinent metabolites was identified by using FOCUS step 1 PECsw.

For honeybees, acute toxicity data and larval single exposure data were available with bromoxynil octanoate and/or the representative formulation. For bromoxynil, acute and chronic data on honeybees and an acute contact toxicity study on bumblebees were available. Only the acute risk assessment was conducted according to the European Commission Guidance (2002a). Based on that assessment, low acute risk was identified for honey bees exposed to bromoxynil octanoate and bromoxynil in the treated crop. As that guidance (2002a) does not provide a risk assessment scheme which is able to use the chronic toxicity data for adult honeybees and the honeybee brood and larvae data and it only covers the exposure to the treated crops, the risk to adult honeybees from chronic toxicity and the risk to bee brood and larvae as well as the risk posed to bees from other relevant exposure routes, was not performed.

As regards non-target arthropods a high in-field risk was identified to the two standard species (*Aphidius rhopalosiphi* and *Typhlodromus pyri*). The risk assessment for *A. rhopalosiphi* was assessed as low based on extended laboratory studies. Aged residue studies were available on *T. pyri*.

The uncertainties related to the effects observed in the aged residue study with *T. pyri* were discussed at the Peer Review experts’ meeting 154. Considering the tested application rate, the type of formulation and the observed effects which were below 50% at 42 days, the low off-field risk, the experts agreed that overall a low in-field risk to non-target arthropods can be, concluded. A toxicity study with the species *Trichogramma cacocemia* was available showing very high effects on mortality and parasitism. The study design was, however, old and many uncertainties in the results were identified at the Peer Review experts’ meeting 154. Therefore, it was agreed not to repeat the study considering the risk to that species to be covered by the standard species (*Aphidius* sp.).

Toxicity data on earthworms were available on bromoxynil octanoate, bromoxynil and the representative formulation. When performing the risk assessment, a low risk was identified for bromoxynil octanoate and bromoxynil but a high risk was identified for the formulation. A field study conducted in Germany was available and the results were discussed at the Peer Review experts’ meeting 154. Based on the observations, the experts concluded a low risk in situations represented by the field study. However, its representativeness for other regions in EU needs to be further investigated at member states level.
Low risk to soil macroorganisms other than earthworms and to soil microorganisms was identified.

Low risk to soil organisms was identified for all the pertinent soil metabolites.

Toxicity data on seedling emergence and vegetative vigour of different non-target terrestrial plants were available. The probabilistic risk assessment was discussed at the Peer Review experts’ meeting 154. Based on the Species Sensitivity Distribution (SSD), low risk was identified to non-target terrestrial plants when applying mitigation measures up to 5 m no-spray buffer zone for all the representative uses.

A study retrieved through the systematic literature search showed effects on mortality, after 7 days exposure to a formulated product of bromoxynil octanoate (containing 31.7% bromoxynil octanoate) of terrestrial life stages of amphibians (i.e. frogs *Rana temporaria*) at an application rate according to the GAP. Although for some aspects, the study design can be considered worst case (e.g. overspray, lack of shelter) at the Peer Review experts’ meeting 154, the experts discussed and agreed that application of bromoxynil octanoate can overlap with frogs’ migration and therefore effects on amphibian populations could be detrimental. In the absence of a suitable risk assessment scheme for amphibians, a risk assessment for terrestrial life stages of amphibians cannot be performed.

On the basis of the available data, the risk was considered low for organisms involved in biological methods for sewage.

With regard to the potential for endocrine disruption of bromoxynil octanoate and bromoxynil, a data gap was set in Section 2 for further mechanistic data elucidating the potential thyroidal pathway. In the specific case of bromoxynil (both ester and bromoxynil), considering the potential pathway, it is uncertain whether the risk assessment for fish also covers amphibians. Therefore, the experts at the Peer Review experts’ meeting 154 agreed to identify a data gap for further investigating effects on amphibians (i.e. amphibians metamorphosis assay (AMA)).
6. Overview of the risk assessment of compounds listed in residue definitions triggering assessment of effects data for the environmental compartments (Tables 1–4)

Table 1: Soil

| Compound (name and/or code) | Persistence | Ecotoxicology |
|-----------------------------|-------------|---------------|
| Bromoxynil octanoate        | Very low to low persistence | Low risk to soil organisms |
|                            | Single first-order DT<sub>50</sub> 0.15–2.26 days (DT<sub>90</sub> 0.48–7.53 days; laboratory conditions 20–22°C, 8.1–41.9% MWHC soil moisture) | |
| Bromoxynil                  | Very low to low persistence | Low risk to soil organisms |
|                            | Single first-order DT<sub>50</sub> 0.18–7.28 days (DT<sub>90</sub> 0.60–24.17 days; laboratory conditions 20–22°C, 8.2–41.9% MWHC soil moisture) | |
| 3,5-Dibromo-4-hydroxybenzamide (M01) | Very low to low persistence | Low risk to soil organisms |
|                            | Single first-order DT<sub>50</sub> 0.33–1.51 days (DT<sub>90</sub> 1.08–5.03 days; laboratory conditions 20–22°C, 8.2–41.9% MWHC soil moisture) | |
| 3,5-Dibromo-4-hydroxybenzoic acid (M02) | Very low to low persistence | Low risk to soil organisms |
|                            | Single first-order and biphasic DT<sub>50</sub> 0.08–2.46 days (DT<sub>90</sub> 0.49–8.17 days; laboratory conditions 20–22°C, 15.8–32.1% MWHC soil moisture) | |

DT<sub>50</sub>: period required for 50% dissipation; DT<sub>90</sub>: period required for 90% dissipation; MWHC: maximum water-holding capacity.

Table 2: Groundwater

| Compound (name and/or code) | Mobility in soil | > 0.1 μg/L at 1 m depth for the representative uses<sup>(a)</sup> | Pesticidal activity | Toxicological relevance |
|-----------------------------|-----------------|-------------------------------------------------------------|--------------------|------------------------|
| Bromoxynil octanoate        | Immobile K<sub>Foc</sub> 8,751–32,540 mL/g                 | No                | Yes                | Yes                   |
| Bromoxynil                  | High to medium mobility K<sub>Foc</sub> 57–256 mL/g pH dependence | No                | Yes                | Yes                   |
| 3,5-Dibromo-4-hydroxybenzamide (M01) | Very high to medium mobility K<sub>Foc</sub> 32–281 mL/g pH dependence | No                | No                 | Assessment not triggered (no data) |
| 3,5-Dibromo-4-hydroxybenzoic acid (M02) | High to medium mobility K<sub>Foc</sub> 68–371 mL/g pH dependence | No                | No                 | Assessment not triggered (90-day rat NOAEL 100 mg/kg bw per day; maternal and developmental NOAEL in rats 150 mg/kg bw per day) |

K<sub>Foc</sub>: Freundlich organic carbon adsorption coefficient; NOAEL: no observed adverse effect level; bw: body weight.
(a): FOCUS scenarios or relevant lysimeter.
### Table 3: Surface water and sediment

| Compound (name and/or code) | Ecotoxicology                           |
|----------------------------|-----------------------------------------|
| Bromoxynil octanoate       | Data gap for aquatic plants and algae  |
| Bromoxynil                 | Low risk to aquatic organisms           |
| 3,5-dibromo-4-hydroxybenzamide (M01) | Low risk to aquatic organisms           |
| 3,5-dibromo-4-hydroxybenzoic acid (M02) | Low risk to aquatic organisms           |
| 3-bromo-4-hydroxybenzonitrile (M03) | Low risk to aquatic organisms           |
| 4-hydroxybenzonitrile (M06) | Low risk to aquatic organisms           |
| 3-bromo-4,5-di hydroxybenzonitrile (M12) | Low risk to aquatic organisms           |
| 3,4-dihydroxy benzonitrile (M13) | Low risk to aquatic organisms           |
| 2-bromo-4-cyanophenyl octanoate (M09) | Low risk to aquatic organisms           |

### Table 4: Air

| Compound (name and/or code) | Toxicology                                      |
|----------------------------|-------------------------------------------------|
| Bromoxynil octanoate       | Rat LC<sub>50</sub> inhalation BXO: 0.72 mg/L. Toxic if inhaled |
| Bromoxynil                 | Rat LC<sub>50</sub> inhalation BXP: 0.15 mg/L. Fatal if inhaled |

LC<sub>50</sub>: lethal concentration, median.
7. Data gaps

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

- Additional validation data for the confirmatory method for the method for residues in animal matrices (relevant for all representative uses evaluated, submission date proposed by the applicant: unknown; see Section 1).
- Mechanistic data investigating whether thyroid toxicity is endocrine mediated by investigating possible binding to transthyretin (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- A new wheat metabolism study compliant with the representative use on cereals (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Determination of residues in pollen and bee products for human consumption, taken up by honeybees from crops at blossom (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- The consumer risk assessment from the consumption of water could not be finalised, while satisfactory information was not available to address the effect of water treatment processes on the nature of the residues that might be present in surface water, when surface water is abstracted for drinking water (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 4).
- EC_{10} and EC_{20} should be calculated, when possible, and reported together with the NOEC (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the risk to birds and mammals when exposed to metabolites of bromoxynil octanoate and bromoxynil formed in plants (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 3 and 5).
- Further information to address the long-term risk to large herbivorous and small omnivorous mammals (relevant for the representative on cereals and all representative use, respectively; submission date proposed by the applicant: unknown; see Section 5).
- Further data to address the risk to algae and aquatic plants, including rooted macrophytes when exposed to bromoxynil octanoate (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Suitable risk assessment according to EFSA (2013) should be presented for (i) chronic data with adult honeybees, (ii) data on larvae and brood, (iii) all relevant exposure routes (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Further data to investigate effects on amphibians (i.e AMA) (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).

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

- Operators should use personal protective equipment (coverall and sturdy footwear, and gloves for mixing/loading and application) according to the German Model (see Section 2).
- Workers should use personal protective equipment (gloves) according to the EUROPOEM II (see Section 2).
- Risk mitigation up to 25 m no-spray buffer zone was required to identify low risk to aquatic organisms for bromoxynil octanoate and up to 5 m no-spray buffer zone and 10 m vegetative buffer strip for bromoxynil (see Section 5).
- Risk mitigation up to 5 m no-spray buffer zone was required to identify low risk to non-target terrestrial plants (see Section 5).
9. **Concerns**

9.1. **Issues that could not be finalised**

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

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

1) The consumer risk assessment could not be finalised for products of animal origin considering the outstanding data to perform a comprehensive livestock exposure assessment (see Section 3).

2) The consumer risk assessment from the consumption of water could not be finalised, whilst satisfactory information was not available to address the effect of water treatment processes on the nature of the residues that might be present in surface water, when surface water is abstracted for drinking water (see Section 4).

3) The risk assessment to aquatic plants when exposed to bromoxynil octanoate could not be finalised due to the lack of suitable data (see Section 5).

9.2. **Critical areas of concern**

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

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

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

4) Bromoxynil and its esters are currently classified as toxic for reproduction category 2, in accordance with the provisions of Regulation (EC) No 1272/2008, and toxic effects on the endocrine organs have been observed in the available data (i.e. thyroid toxicity in Fischer F344 rats); therefore, the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine disrupting properties may be met. Sufficient information is not available to exclude an endocrine disruption potential of bromoxynil and its esters (See Section 2).

5) Bromoxynil and its esters are proposed to be classified as toxic for reproduction category 1B, in accordance with the provisions of Regulation (EC) No 1272/2008 (see Section 2) and a critical area of concern is identified with regard to the approval criteria, Annex II, Point 3.6.4 of Regulation (EC) No. 1107/2009 (see Section 2).

6) High long-term risk after dietary exposure was identified to wild mammals for all the representative uses (see Section 5).

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7 Commission Regulation (EU) No 546/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards uniform principles for evaluation and authorisation of plant protection products. OJ L 155, 11.6.2011, p. 127–175.
9.3. Overview of the concerns identified for each representative use considered (Table 5)

Table 5: Overview of concerns

| Representative use                              | Maize/ corn (Field) | Spring cereals (Field) | Winter cereals (Field) |
|------------------------------------------------|---------------------|------------------------|------------------------|
| Operator risk                                   | Risk identified     | Assessment not finalised|                        |
| Worker risk                                     | Risk identified     | Assessment not finalised|                        |
| Resident/bystander risk                         | Risk identified     | Assessment not finalised|                        |
| Consumer risk                                   | Risk identified     | Assessment not finalised| X² X² X² |
| Risk to wild non-target terrestrial vertebrates| Risk identified     | X⁶                      | X⁶                     |
| Risk to wild non-target terrestrial organisms other than vertebrates | Risk identified     | Assessment not finalised|                        |
| Risk to aquatic organisms                      | Risk identified     | Assessment not finalised| X³ X³ X³ |
| Groundwater exposure to active substance        | Legal parametric value breached |                        |                        |
| Groundwater exposure to metabolites             | Legal parametric value breached | Parametric value of 10 µg/L breached | Assessment not finalised |

Columns are grey if no safe use can be identified. The superscript numbers relate to the numbered points indicated in Sections 9.1 and 9.2. Where there is no superscript number, see Sections 2-6 for further information.

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**Abbreviations**

| Acronym | Description |
|---------|-------------|
| AAOEL   | acute acceptable operator exposure level |
| ADI     | acceptable daily intake |
| AOEL    | acceptable operator exposure level |
| AR      | applied radioactivity |
| ARfD    | acute reference dose |
bw: body weight
CAS: Chemical Abstracts Service
DT$_{50}$: period required for 50% dissipation (define method of estimation)
DT$_{90}$: period required for 90% dissipation (define method of estimation)
EC: emulsifiable concentrate
EC$_{50}$: effective concentration
ECHA: European Chemicals Agency
EEC: European Economic Community
EUROPOEM: European Predictive Operator Exposure Model
FAO: Food and Agriculture Organization of the United Nations
FIR: food intake rate
FOCUS: Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP: Good Agricultural Practice
GC-ECD: gas chromatography with electron capture detector
GC-MS: gas chromatography–mass spectrometry
HPLC–MS/MS: high performance liquid chromatography with tandem mass spectrometry
ISO: International Organization for Standardization
IUPAC: International Union of Pure and Applied Chemistry
JMPR: Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)

$K_{Foc}$: Freundlich organic carbon adsorption coefficient
LC$_{50}$: lethal concentration, median
LC–MS/MS: liquid chromatography with tandem mass spectrometry
LOAEL: lowest observable adverse effect level
LOQ: limit of quantification
MRL: maximum residue level
MWHC: maximum water-holding capacity
NOAEL: no observed adverse effect level
NOEC: no observed effect concentration
OECD: Organisation for Economic Co-operation and Development
PEC: predicted environmental concentration
PEC$_{air}$: predicted environmental concentration in air
PEC$_{gw}$: predicted environmental concentration in groundwater
PEC$_{sed}$: predicted environmental concentration in sediment
PEC$_{soil}$: predicted environmental concentration in soil
PEC$_{sw}$: predicted environmental concentration in surface water
PHI: preharvest interval
PPAR$\alpha$: Peroxisome proliferator-activated receptor alpha
PPE: personal protective equipment
RAR: Renewal Assessment Report
RUD: residue per unit dose
SFO: single first-order
SMILES: simplified molecular-input line-entry system
SSD: species sensitivity distribution
TK: technical concentrate
TRR: total radioactive residue
UF: uncertainty factor
WHO: World Health Organization
Appendix A – List of end points for the active substance and the representative formulation

Appendix A can be found in the online version of this output (‘Supporting information’ section): https://doi.org/10.2903/j.efsa.2017.4790
### Appendix B – Used compound codes

| Code/trivial name | Chemical name/SMILES notation | Structural formula |
|-------------------|-------------------------------|--------------------|
| **M01**<br>3,5-Dibromo-4-hydroxybenzamide | 3,5-Dibromo-4-hydroxybenzamide<br>Brc1cc(cc(Br)c1O)C(N)=O | ![Structural formula](image1.png) |
| **M02**<br>3,5-Dibromo-4-hydroxybenzoic acidDBHA | 3,5-Dibromo-4-hydroxybenzoic acid<br>Brc1cc(cc(Br)c1O)C(=O)O | ![Structural formula](image2.png) |
| **M03**<br>3-Bromo-4-hydroxybenzonitrileDesbromoxynil | 3-Bromo-4-hydroxybenzonitrile<br>Oc1ccc(C#N)cc1Br | ![Structural formula](image3.png) |
| **M06**<br>4-Hydroxybenzonitrile | 4-Hydroxybenzonitrile<br>N#Cc1ccc(O)cc1 | ![Structural formula](image4.png) |
| **M12**<br>3-Bromo-4,5-dihydroxybenzonitrile | 3-Bromo-4,5-dihydroxybenzonitrile<br>Oc1cc(cc(Br)c1O)C#N | ![Structural formula](image5.png) |
| **M13**<br>3,4-Dihydroxybenzonitrile | 3,4-Dihydroxybenzonitrile<br>Oc1ccc(C#N)cc1O | ![Structural formula](image6.png) |
| **M09**<br>2-Bromo-4-cyanophenyl octanoate | 2-Bromo-4-cyanophenyl octanoate<br>Brc1cc(ccc1OC(-O)CCCCCCC)C#N | ![Structural formula](image7.png) |
| Code/trivial name | Chemical name/SMILES notation | Structural formula |
|------------------|--------------------------------|--------------------|
| 2,6-Dibromohydroquinone glucoside | 3,5-Dibromo-4-hydroxyphenyl α-glucopyranoside <br> BrC1cc(cc(Br)c1O)OC2O[C@H](CO) [<br> [C@@H](O)[C@H][O][C@H]2O | ![Structural formula](image) |

**SMILES**: simplified molecular-input line-entry system.