CONCLUSION ON PESTICIDE PEER REVIEW

Conclusion on the peer review of the pesticide risk assessment of the active substance bitertanol[1]

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SUMMARY

Bitertanol is one of the 79 substances of the third stage part A of the review programme covered by Commission Regulation (EC) No 1490/2002[3], as amended by Commission Regulation (EC) No 1095/2007[4]. In accordance with the Regulation, at the request of the Commission of the European Communities (hereafter referred to as 'the Commission'), the EFSA organised a peer review of the initial evaluation, i.e. the Draft Assessment Report (DAR), provided by the United Kingdom being the designated rapporteur Member State (RMS). The peer review process was subsequently terminated following the applicant's decision, in accordance with Article 11e, to withdraw support for the inclusion of bitertanol in Annex I to Council Directive 91/414/EEC.

Following the Commission Decision of 05 December 2008 (2008/934/EC)[5] concerning the non-inclusion of bitertanol in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing that substance, the applicant (Bayer CropScience) made a resubmission application for the inclusion of bitertanol in Annex I in accordance with the provisions laid down in Chapter III of Commission Regulation (EC) No. 33/2008[6]. The resubmission dossier included further data in response to the issues identified in the DAR.

In accordance with Article 18 of Commission Regulation (EC) No. 33/2008, the United Kingdom being the designated RMS, submitted an evaluation of the additional data in the format of an Additional Report. The Additional Report was received by the EFSA on 27 November 2009.

In accordance with Article 19 of Commission Regulation (EC) No. 33/2008, the EFSA distributed the Additional Report to Member States and the applicant for comments on 01 December 2009. The EFSA collated and forwarded all comments received to the Commission on 20 January 2010.

In accordance with Article 20, following consideration of the Additional Report, the comments received, and where necessary the DAR, the Commission requested the EFSA to conduct a focused peer review in the areas of mammalian toxicology and ecotoxicology and deliver its conclusions on bitertanol.

The conclusions laid down in this report were reached on the basis of the evaluation of the representative uses of bitertanol as a seed-treatment fungicide on winter wheat, winter barley, rye and

1 On request from the European Commission, Question No EFSA-Q-2010-00130, issued on 06 October 2010

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3 OJ L224, 21.08.2002, p.25

4 OJ L 246, 21.9.2007, p. 19

5 OJ L 333, 11.12.2008, p. 11

6 OJ L 15, 18.01.2008, p.5

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triticale as proposed by the applicant. Full details of the representative uses can be found in Appendix A to this report.

The degradation of the two enantiomers making up each diastereoisomer pair in plants, animals and the environment, and the possible impact on the toxicity, the consumer risk assessment, and the environment were not investigated in the studies submitted in the dossier and needs to be addressed.

Data gaps were identified in the section analytical methods.

In the mammalian toxicology section, one data gap was identified for the assessment of the toxicological relevance of two impurities, triggering an area of concern in relation to the lack of compliance of the batches used in the toxicological studies with the technical specification.

Fort the representative use, the residue definition for monitoring and risk assessment was not finalised. Since bitertanol was not present above the LOQ in consumable crop parts, no risk was identified for consumers from exposure to the parent compound. However, insufficient data are available to conduct a human and animal intake risk assessment for residues of triazole derivative metabolites resulting from the representative use of bitertanol in cereals.

Concerning the environmental fate and behaviour of bitertanol, no specific data gaps were identified in respect of the representative use assessed. No areas of concern were identified with respect to the potential for groundwater contamination.

A data gap was identified to submit information on the composition of the batches used in the ecotox tests including an assessment of the biological activity of the two diastereomers.

A critical area of concern was identified for the acute and short-term risk to granivorous birds as well as for the long-term-risk to mammals. Further data are required to address the concerns highlighted.

Due to the time of application (autumn) a long-term risk assessment for granivorous birds was not conducted. However, to address the long-term risk for birds which may breed in the autumn a data gap was identified. For the representative use, a low risk was identified for aquatic organisms, bees, non-target arthropods, non-target soil macro and micro- organisms, terrestrial non-target plants and biological methods of sewage treatment plants.

KEY WORDS

bitertanol, peer review, risk assessment, pesticide, fungicide

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BACKGROUND

Legislative framework

Commission Regulation (EC) No 1490/2002[7], as amended by Commission Regulation (EC) No 1095/2007[8] lays down the detailed rules for the implementation of the third stage of the work programme referred to in Article 8(2) of Council Directive 91/414/EEC. This regulates for the European Food Safety Authority (EFSA) the procedure for organising, upon request of the Commission of the European Communities (hereafter referred to as 'the Commission'), a peer review of the initial evaluation, i.e. the Draft Assessment Report (DAR), provided by the designated rapporteur Member State.

Commission Regulation (EC) No 33/2008[9] lays down the detailed rules for the application of Council Directive 91/414/EEC for a regular and accelerated procedure for the assessment of active substances which were part of the programme of work referred to in Article 8(2) of Council Directive 91/414/EEC but which were not included in Annex I. This regulates for the EFSA the procedure for organising the consultation of Member States and the applicant(s) for comments on the Additional Report provided by the designated RMS, and upon request of the Commission the organisation of a peer review and/or delivery of its conclusions on the active substance.

Peer review conducted in accordance with Commission Regulation (EC) No 1490/2002

Bitertanol is one of the 79 substances of the third stage part A of the review programme covered by Commission Regulation (EC) No 1490/2002, as amended by Commission Regulation (EC) No 1095/2007. In accordance with the Regulation, at the request of the Commission, the EFSA organised a peer review of the DAR provided by the designated rapporteur Member State, the United Kingdom which was received by the EFSA on 05 April 2005 (United Kingdom 2005)

The peer review was initiated on 23 March 2006 by dispatching the DAR to Member States and the applicant Bayer CropScience for consultation and comments. In addition, the EFSA conducted a public consultation on the DAR. The comments received were collated by the EFSA and forwarded to the RMS for compilation and evaluation in the format of a Reporting Table. The Reporting Table containing the RMS' evaluation of the comments in column 3 was further considered by the EFSA, resulting in a conclusion in column 4.

The peer review process was subsequently terminated following the applicant's decision, in accordance with Article 11e, to withdraw support for the inclusion of bitertanol in Annex I to Council Directive 91/414/EEC.

Peer review conducted in accordance with Commission Regulation (EC) No 33/2008

Following the Commission Decision of 05 December 2008 (2008/934/EC)[10] concerning the non-inclusion of bitertanol in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing that substance, the applicant Bayer CropScience made a resubmission application for the inclusion of bitertanol in Annex I in accordance with the provisions laid down in Chapter III of Commission Regulation (EC) No. 33/2008. The resubmission dossier included further data in response to the issues identified in the DAR. In accordance with Article 18, the United Kingdom being the designated RMS, submitted an evaluation of the additional data in the format of an Additional Report. The Additional Report was received by the EFSA on 27 November 2009 (United Kingdom 2009)

[7] OJ L224, 21.08.2002, p.25
[8] OJ L246, 21.9.2007, p.19
[9] OJ L 15, 18.01.2008, p.5
[10] OJ L 333, 11.12.2008. p. 11

In accordance with Article 19, the EFSA distributed the Additional Report to Member States and the applicant for comments on 01 December 2009. In addition, the EFSA conducted a public consultation on the Additional Report. The EFSA collated and forwarded all comments received to the Commission on 20 January 2010. At the same time, the collated comments were forwarded to the RMS for compilation in the format of a Reporting Table. The applicant was invited to respond to the comments in column 3 of the Reporting Table. The comments and the applicant's' response was evaluated by the RMS in column 3.

In accordance with Article 20, following consideration of the Additional Report, the comments received, and where necessary the DAR, the Commission decided to further consult the EFSA. By written request, received by the EFSA on 19 February 2010, the Commission requested the EFSA to arrange a consultation with Member State experts as appropriate and deliver its conclusions on bitertanol within 6 months of the date of receipt of the request, subject to an extension of a maximum of 90 days where further information were required to be submitted by the applicant in accordance with Article 20(2).

The scope of the peer review and the necessity for additional information, not concerning new studies, to be submitted by the applicant in accordance with Article 20(2), was considered in a telephone conference between the EFSA, the RMS, and the Commission on 15 March 2010. The applicant was also invited to give its view on the need for additional information. On the basis of the comments received, the applicant's response to the comments, and the RMS' subsequent evaluation thereof, it was concluded that the EFSA should organise a consultation with Member State experts in the areas of mammalian toxicology and ecotoxicology and that further information should be requested from the applicant in the areas of physical-chemical properties, mammalian toxicology 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 consultation with Member State experts, and the additional information to be submitted by the applicant, were compiled by the EFSA in the format of an Evaluation Table.

The conclusions arising from the consideration by the EFSA, and as appropriate by the RMS, of the points identified in the Evaluation Table, together with the outcome of the expert discussions 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 September 2010.

This conclusion report summarises the outcome of the peer review of the risk assessment on the active substance and the representative formulation evaluated on the basis of the representative uses as a seed-treatment fungicide on winter wheat, winter barley, rye and triticale, as proposed by the applicant. A list of the relevant end points for the active substance as well as the formulation is provided in Appendix A. In addition, a key supporting document to this conclusion is the Peer Review Report (EFSA, 2010), 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:

- the comments received on the DAR and the Additional Report,
- the Reporting Table (revision 1-1, 17 February 2010)
- the Evaluation Table (6 October 2010)
- the report(s) of the scientific consultation with Member State experts (where relevant).

Given the importance of the DAR and the Additional Report including its addendum (compiled version of September 2010, United Kingdom 2010) containing all individually submitted addenda) and the Peer Review Report , both documents are considered respectively as background documents A and B to this conclusion.

THE ACTIVE SUBSTANCE AND THE FORMULATED PRODUCT

Bitertanol is the ISO common name for (1*RS*,2*RS*;1*RS*,2*SR*)-1-(biphenyl-4-yloxy)-3,3-dimethyl-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (20:80 ratio of (1*RS*,2*RS*)- and (1*RS*,2*SR*)-isomers) (IUPAC).

The representative formulated product for the evaluation was 'Sibutol', a flowable concentrate for seed treatment (FS), containing 375 g/l bitertanol and 23 g/l fuberidazole, registered under different trade names in Europe.

The representative uses evaluated comprise seed treatment on autumn sown cereals to control a range of fungal pathogens. The application rate has been reduced in comparison to the original submission. Full details of the GAP can be found in the list of end points in Appendix A.

As indicated above, bitertanol is a mixture of 4 isomers (2 diastereoisomer pairs) The possible preferential metabolism/degradation of each enantiomer making up each diasteroisomer pair in animals, plants and the environment was not investigated in the studies submitted in the dossier and therefore information on this was not available during the peer review. The possible impact of each enantiomer making up each diastereoisomer pair on the toxicity, the worker assessment, the consumer risk assessment and the environment could not be evaluated, with the exception that risk assessments could be concluded when residues were not detectable or estimated to be negligibly low, consequent to the representative use evaluated. A general data gap, applicable for sections 2, 3, 4 and 5 was therefore identified to address the impact of the isomeric composition of the active substance on the risks that need to be assessed. The metabolites / transformation products that retain the chiral centres would also need to be considered if other uses will be evaluated.

CONCLUSIONS OF THE EVALUATION

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

The minimum purity of bitertanol technical material is 970 g/kg. The content of (1*RS*,2*RS*)- and (1*RS*,2*SR*)-isomers is 10 – 20% and 80 - 90%, respectively. The active substance content of the technical material is meeting the minimum declared bitertanol content of 900 g/kg of the FAO specification AGP: CP/361 (1998). However for the isomer ranges in the FAO specification namely the ratio of the isomers *RR* + *SS* of 15 to 30 % and *RS* + *SR* of 70 to 85 % are not meeting the range for the RS + SR and no justification is given.

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 bitertanol or the respective formulation. The main data regarding the identity of bitertanol and its physical and chemical properties are given in Appendix A.

Adequate analytical methods are available for the determination of bitertanol and the impurities in the technical material and for the determination of the active substance in the representative formulation. Residues of bitertanol in food of plant and animal origin can be monitored with the German modular multi-method DFG S19, however a data gap was identified for additional validation data on the confirmatory methods for residues of bitertanol in treated plants. Although the same issue was identified with the confirmatory method for animal products it is not a data gap as no MRLs are proposed and therefore the methods are not necessary. Adequate analytical methods are available for monitoring the residues of bitertanol in soil and water, however a data gap was identified for a method which is able to quantify residues of bitertanol with a limit of quantification of 3 µg/m^3 in air. Analytical methods for the determination of residues in body fluids and tissues are not required as bitertanol is not classified as toxic or highly toxic.

2. Mammalian toxicity

Bitertanol was discussed during the PRAPeR 79 expert meeting on mammalian toxicology. Based on a lack of assessment of the toxicological relevance of two impurities in the DAR and AR, the technical specification cannot be considered as covered by the batches used in the toxicological studies and a data gap has been identified.

Based on the available results, bitertanol has a low order of acute toxicity via the oral, dermal and inhalation routes. It is not irritant or sensitising to the skin, and slightly eye irritant. In short-term toxicity studies with rats, the liver was the most sensitive organ and reduced body weight was the most sensitive effect, resulting in a NOAEL of 12 mg/kg bw/day. In dogs, the most sensitive species, the target organs were the adrenals (increased severity and incidence of fatty vacuolisation of the adrenal cortex, compared to historical control data), the liver, the eye (corneal keratitis secondary to conjunctivitis, cataracts), the skin (inflammation) and the thymus. Two different NOAELs were set by the experts for the dog studies: 1.0 mg/kg bw/day for the 90-day and 12 month studies, and 0.3 mg/kg bw/day for the 2-year dog study. Based on the available studies, it can be concluded that bitertanol has no genotoxic potential, and no evidence of carcinogenicity was observed in rats or mice. The long-term NOAEL in rats is 4.9 mg/kg bw/d based on reduced body weight gain and increased adrenal weight, whereas the long-term NOAEL in mice is 25 mg/kg bw/day based on reduced body weight gain and liver effects. In the rat multigeneration study, the agreed parental NOAEL is 2.0 mg/kg bw/d based on significantly decreased body weight gain values over the three generations at 100 ppm (mid-dose); the NOAEL for the reproductive parameters is 10.0 mg/kg bw/day based on reduced litter size at birth; and the NOAEL for the offspring is 10.0 mg/kg bw/day based on reduced body weight gain during lactation and decreased pup viability. In the developmental toxicity studies, malformations were observed in rats and rabbits, leading to the proposed classification as **Repro.Cat.2, R61** *May cause harm to the unborn child*. From the rat studies, the maternal and developmental NOAEL is 10 mg/kg bw/day based on a reduced body weight gain, an increased number of stunted foetuses and skeletal variations. From the rabbit studies, the maternal and developmental NOAEL is 30 mg/kg bw/day based on reduced body weight gain, clinical signs and reduced food intake; as well as an increased incidence of abortions/resorptions, a decreased foetal weight and an increased incidence of stunted foetuses. The NOAEL for teratogenicity is the same for both rat and rabbit, i.e. 30 mg/kg bw/day. There was no specific neurotoxic effect in a 13-week neurotoxicity study with rats, as well as no evidence of treatment-related ophthalmological findings.

All reference values were derived with the use of a safety factor of 100, providing a margin of safety higher or equal to 1000 with regard to developmental findings (malformations triggering R61). Consequently, the agreed **Acceptable Daily Intake** (ADI) is 0.003 mg/kg bw/day, based on the 2-year dog study; the agreed **Acceptable Operator Exposure Level** (AOEL) is 0.01 mg/kg bw/day, based on the 1-year dog study; and the agreed **Acute Reference Dose** (ARfD) is 0.01 mg/kg bw/day based on the 90-day dog study (decreased body weight during the first week).

Based on the available data in the bitertanol dossier, and including an additional study discussed during PRAPeR 14 for 1,2,4-triazole and showing a lower NOAEL (Young, 2005), reference values were agreed for the triazole metabolites. For **1,2,4-triazole**, the agreed ADI is 0.02 mg/kg bw/d based on the 2-generation rat study (Young, 2005; NOAEL 17, SF 1000); and the agreed ARfD is 0.06 mg/kg bw based on the rat developmental study (NOAEL 30, SF 500). For **triazole acetic acid**, the ADI and ARfD of 1,2,4-triazole were considered applicable due to the limited database available. For **triazole alanine**, the agreed ADI and ARfD is 0.1 mg/kg bw/d based on the rat developmental study (NOAEL 100, SF 1000).

For operators during the seed treatment, the maximum exposure from the bagging and mixing/calibration/cleaning activities is below the AOEL. This reflects an operator wearing a long sleeved jacket and long trousers for all tasks, protective gloves for all tasks except bagging and an impermeable coverall in addition for the cleaning operation. For workers during handling of treated seed and contaminated material, they have to wear suitable protective clothing (coverall) and suitable respiratory protective equipment is required to have an exposure level at the AOEL. Predicted

exposures for bystanders are below the AOEL, even considering the worst-case estimates for fork lift truck drivers in seed treatment plants.

Pending on further identification of the ratio of diastereoisomers/enantiomers the workers are exposed to, and on further assessment of the relative toxicity of the different diastereoisomers, the use of the AOEL for the worker exposure estimates (as agreed for the ratio of isomers/enantiomers in the technical specification) might need to be reconsidered since the worker exposure is already up to 100% of the AOEL with the use of coverall and respiratory protective equipment. However in the situation that the treated seed is stored properly (dry and in the dark) the expectation would be that the isomer ratios would be unlikely to change.

3. Residues

The metabolism of bitertanol has been investigated using foliar applications to apple, tomato, cotton and peanuts, and seed treatment in wheat, representing the crop categories fruits, cereals, and pulses/oilseeds. Bitertanol is a mixture of two diastereomeric pairs of enantiomers (4 bitertanol isomers). The plant metabolism studies were conducted with bitertanol containing variable diastereoisomer ratios (ranging between 56:44 and 80:20). The ratio of the enantiomers in each diastereomer was not reported. As for the representative use in cereals, the regulatory dossier does not provide information on the behaviour of each individual bitertanol isomer. As a result, all residues reported for cereals as bitertanol in this conclusion are for the sum of the two diastereomeric pairs of enantiomers. No further information on isomers is considered necessary for the consumer risk assessment in terms of the representative use because of the insignificant residues of parent bitertanol.

As for the age of some of the submitted metabolism studies, identification of metabolites was conducted only for the most abundant compounds of the terminal residue, and not in all plant parts relevant for human and animal consumption. No identification was attempted in oilseed seeds (cotton seed and peanuts). Based on the available data, metabolism seems to be similar in fruit and in leafy crop parts upon a foliar treatment, with the major constituents of the residue being unchanged bitertanol (75-99% of the TRR). However, in seed treated cereals the triazole derivative metabolites (TDM), in particular triazole alanine (TA), accounted for 50% to 66% of the TRR in cereal grains and triazole acetic acid (TAA) for 22-34% of the TRR. Bitertanol was not detected in the grain, and only in very low amounts in straw, where in addition bitertanol benzoic acid represented 13% of the TRR. As earlier observed for some of the triazole pesticide active substances, metabolism appears to be different among crop categories. Hence, a global plant residue definition is difficult to conclude. While bitertanol alone might be appropriate for inclusion in the residue definition for monitoring and risk assessment for fruit and leafy crops, bitertanol is virtually not present in seed treated cereals. However, given the relevance of the TDM for the representative use in cereals (present in the grain at much higher levels than bitertanol and of toxicological concern for the consumer), the residue definition for risk assessment needs to consider the TDM. The metabolite profile in rotational crops was only investigated with biphenyl labelled bitertanol and thus a conclusion in terms of potential uptake of TDM residues is currently not possible, though uptake of TDM is expected to occur in rotational crops. Currently, the plant residue definition for the risk assessment can not be finalised until the necessary data are available to fully address the nature and magnitude of residues resulting from the representative use of bitertanol in cereals.

The wheat metabolism study indicated bitertanol is not expected to be present in the grain and to occur in significant amounts in straw. Yet, all reported supervised residue trials in cereals for the Northern European region analyse for bitertanol alone, and an MRL for bitertanol in cereals was proposed at the LOQ level (0.05* mg/kg). A data gap was set for residue trials in cereals in Southern Europe since no trials were submitted. However, the residue levels of TDM were not reported in any of the available residue trials, but TDM are expected to occur in significant amounts in the grain. In a hydrolysis study simulating processing conditions, bitertanol is not degraded; however data on whether TDM will be degraded in processing are not available.

In terms of the representative use in cereals exposure of livestock to bitertanol is below the trigger value to conduct livestock studies, and it was not necessary to propose MRLs for bitertanol in livestock tissues. However data are not available to assess whether animal exposure to the TDM is significant. Studies with phenyl labelled bitertanol in cow and chicken are available but not considered suitable to clarify the fate of TDM in livestock. It is currently unknown whether significant residues of TDM may occur in food of animal origin.

The consumer chronic and short-term intakes estimated for bitertanol using the UK or EFSA PRIMo models are less than 20% of the proposed ADI, and less than 8% of the ARfD. However, these estimates are provisional as the contribution of the TDM, likely to be present in significant amount in cereals and possibly also in commodities of rotational crops and of animal origin, was not taken into account. Insufficient data is available to conduct a human and animal intake risk assessment for residues of TDM resulting from the representative use of bitertanol. Therefore a data gap was identified for data and information permitting the assessment of consumer exposure to TDM in primary crops and rotational crops, including their processed products, and products of animal origin.

4. Environmental fate and behaviour

The route and rate of degradation in soil of bitertanol was investigated in 6 soils in the laboratory under dark aerobic conditions with the test substance radiolabelled in different positions. In an experiment with biphenyl-labelling in one soil, both diastereoisomer pairs of bitertanol were demonstrated to decline at the same rate (the initial ratio A:B being 57:43), but information was not available on the behaviour of each diastereoisomer pair (initial ratio 80:20) in the environment from the other two studies performed with the phenyl and triazole labelling. The available studies provide no information on the behaviour of each enantiomer that constitutes each diastereoisomer pair, as chiral chromatographic techniques were not used in sample analyses. DT_{50} values presented in appendix A are therefore for the sum of all isomers.
Experiments with phenyl-labelling demonstrated a partial oxidation of the biphenyl group leading to the minor (≤0.3% applied radioactivity (AR)) metabolite bitertanol-benzoic acid, M01 as a transient intermediate and finally to carbon dioxide (max. 48-59% AR after 100 days). An experiment with triazole-labelling (1 soil) showed that 1,2,4-triazole[11] is formed as the major metabolite (max. 44% AR after 62 d and declining to 36% AR at study end 120 days). After 120 days, 53% AR was unextractable residues following extensive extraction and mineralisation to carbon dioxide accounted for 1.6-52% AR. Apart from 1,2,4-triazole, no other major metabolite was observed. Unextracted residues were 46% AR at 91 days in the biphenyl labelled experiment, 25-43% AR at 100 days in phenyl labelled experiments and 53% AR after 120 days in the triazole labelled experiment. Bitertanol exhibited low to moderate persistence in soil. 1,2,4-triazole exhibits low persistence in soil. An additional study was performed to investigate the rate of aerobic degradation in soil of triazole acetic acid (M07 or TAA), a metabolite formed from the degradation of 1,2,4-triazole (max. 6.9% AR in an aerobic incubation and up to 50% AR in an anaerobic incubation, both investigations where 1,2,4-triazole was dosed). Triazole acetic acid exhibits low to moderate persistence in soil. Even though further assessment was not performed for this metabolite, it is the EFSA opinion that taking into consideration the application dose of bitertanol and the maximum amount of 1,2,4-triazole (the precursor of TAA) and of triazole acetic acid formed in soil, it is likely that under field conditions triazole acetic acid will only be present in very low amounts. A laboratory soil photolysis study, where [biphenyl-UL-^{14}C]-bitertanol was used, showed that bitertanol is essentially stable to photolysis at the soil surface. Bitertanol exhibits low to slight mobility in soil, while metabolite 1,2,4-triazole exhibits very high to medium mobility in soil. There was no evidence of pH dependence of adsorption for either of these two compounds.

In aerobic natural sediment water systems (laboratory incubations) bitertanol dissipated rapidly from the water phase via partitioning to the sediment. The degradation of bitertanol was characterised by a

[11] The environmental exposure assessment for the metabolite 1,2,4-triazole was based on the proposed set of fate and behaviour end points established at the PRAPeR 12 meeting held on 15-18 January 2007.

relatively high mineralisation rate with up to 49% of carbon dioxide produced after 120 days and by the formation of bound residues (up to 40% AR at 82d). The ratio between the diastereoisomers was not affected. A kinetic re-assessment of the behaviour of bitertanol in the water sediment study was presented in the Additional Report to comply with the FOCUS Degradation Kinetics Guidance Document (FOCUS, 2006). Aqueous photolysis can contribute to the overall dissipation of bitertanol in aquatic systems. The photodegradation products found in the aqueous photolysis study with the phenyl labelling were 4-hydroxy-biphenyl M04 (max. 24.2% AR after 6d), benzoic acid M27 (max. 38.1% AR after 10d) and salicylic acid M28 (max. 15.6% AR after 10d). Because in natural systems partitioning to sediment and degradation by microbial action will be more important it was concluded that photolysis would not be a significant process and therefore an aquatic exposure assessment for these metabolites was not necessary, especially in relation to the seed treatment use assessed. In the Additional Report new predicted environmental concentrations (PEC) in surface water and sediment were submitted to reflect the new kinetic assessments for soil and water/sediment systems, and to reflect the revised GAP proposed. Calculations were based on FOCUS (2001) step 1 and step 2 for bitertanol and metabolite 1,2,4-triazole. Moreover, PEC_{sw} and PEC_{sed} were calculated for bitertanol using the FOCUS (2001) step 3[12].
The necessary groundwater exposure assessments were appropriately carried out using FOCUS (FOCUS, 2000) scenarios and models (PEARL 3.3.3 and PELMO 3.3.2)[13]. The potential for groundwater exposure from the representative uses by bitertanol and its metabolite 1,2,4-triazole above the parametric drinking water limit of 0.1 µg/L, was concluded to be low in geoclimatic situations that are represented by all 9 FOCUS groundwater scenarios.

The PEC in soil, surface water, sediment and groundwater, covering the representative uses assessed as a cereal seed treatment can be found in Appendix A.

5. Ecotoxicology

A data gap was identified to submit information on the composition of the batches used in the ecotoxicology, tests including an assessment of the biological activity of the two diastereoisomers.

A high acute and short-term risk to granivorous birds via dietary exposure was identified at first-tier risk assessment following the Guidance Document (European Commission, 2002a). A long-term risk assessment for birds was not conducted because the representative use (autumn application) was considered to be outside the breeding season for birds in many Member States. However, it was acknowledged that in some Member States (mainly southern Member States) birds may breed in the autumn, hence a data gap was identified during the peer review to provide the long-term risk assessment for granivorous birds in order to address the breeding potential in autumn.

To put the risk into perspective, for small granivorous birds the number of seeds to reach the lethal doses including the safety factor of 10 (i.e. $LD_{50}/10$ and the $LDD_{50}/10$) was estimated by RMS and was found to be relatively small: 41 for acute and >9 for short-term risk. The treated area required to obtain these quantities was also indicated as relatively small from the available data (ca. 1m²). To refine the acute and short-term risk to granivorous birds, residue decline, avoidance studies and ecological data (i.e. radio-tracking data) were submitted. Residue decline was not considered appropriate for the acute and short-term risk assessment. Avoidance studies indicated that seeds treated with bitertanol are not preferentially taken by the tested birds. However, these data did not indicate the response of birds under feeding pressure and in such conditions birds may obtain enough seeds to reach lethal doses. In addition, there was a concern regarding the extrapolation from one bird species to another and from one seed type to another. Therefore, the avoidance data were not used as a

[12] Simulations correctly utilised the agreed Q10 of 2.58 (EFSA 2007) and Walker equation coefficient of 0.7. As the product is not sprayed, the parameterisation at step 3 also followed the pertinent EFSA (2004b) opinion.
[13] Simulations correctly utilised the agreed Q10 of 2.58 (EFSA 2007), Walker equation coefficient of 0.7 and were in accordance with the pertinent EFSA (2004a) opinion.

refinement for the risk assessment. On the basis of a generic field study conducted in Germany, three focal species and related PD and PT refinements were proposed: Skylark (*Alauda arvensis*), Yellowhammer (*Emberiza citrinella*) and Chaffinch (*Fringilla coelebs*). The study was well conducted, only birds consuming seeds were considered in the risk assessment and the worst-case PT were proposed. However, the experts in the PRAPeR TC 37 teleconference questioned the use of PT and PD for acute and short-term risk assessment, especially in light of the small number of seeds and the small area required to reach lethal doses. The representativeness of the focal species for other Member States as well as of the environment of the study site was also questioned. In addition, the refined short-term risk was still assessed as high for small granivorous birds and a high short-term risk was also not excluded for the large granivorous birds (woodpigeon). In an effect field trial no mortalities were recorded over 10 days after drilling of seeds treated with bitertanol, indicating a potential overestimation of the risk in the first-tier risk assessment. However, the highest drilling rate applied in this study was 155 kg seed/ha and did not cover the drilling rate of 230 kg seed/ha foreseen for the representative use. Overall, the experts agreed that the provided dataset is not sufficient to conclude on the risk assessment for birds since several uncertainties still remain. Therefore, further data are required regarding the risk assessment to granivorous birds to address uncertainties in the existing dataset.

A high long-term risk to granivorous mammals via dietary exposure was identified at the first-tier risk assessment following the Guidance Document (European Commission, 2002c). The risk was refined including residue decline data. However the refined TER was still far below the Annex VI trigger (TER= 0.1). The risk was further addressed with a simple population model that assessed the impact of bitertanol on the over-wintering population of woodmice (*Apodemus sylvaticus*). Data had been obtained from a study carried out in the Czech Republic. The applicant modelled the impact of 20% reduction in reproduction, based on the information from a 3-generation rat study. This resulted in an overall impact on the spring population decrease of 0.4-1.9%. The RMS proposed to assume 50% reduction in productivity to take into account a higher theoretical impact on autumn breeding success. The model outcome was a predicted decrease of 4.8% of the spring population. Overall, the experts were concerned about the use of this approach as the only manner to refine the risk, especially in the light of the fact that the first-tier TER was far below the Annex VI trigger. Moreover, the representativeness of the model and of the dataset on which it was based on was questioned. Finally, no information was available to deal with the uncertainties regarding its interpretation (i.e. relevance of a 5% population decline). Therefore, further data are required to address the long-term/reproductive risk to mammals.

Since bitertanol has a log P_{ow} >3 the risk from secondary poising was considered. The risk to earthworm-eating birds and mammals was assessed as low at first-tier level. The risk to fish-eating birds and mammals, and the risk from contaminated drinking water consumption was expected as low for the representative use, due to the negligible exposure (FOCUS step3 PECsw <0.0005µg a.s./L).

Bitertanol is toxic to aquatic organisms. The risk was driven by the chronic toxicity to fish and was high with $FOCUS_{sw}$ step 2 PECsw values. However, a TER exceeding the Annex VI trigger was calculated at $FOCUS_{sw}$ step 3, indicating a low risk to aquatic organisms for all scenarios. Bitertanol may be a potential endocrine disruptor for fish. However, for the representative use the exposure of the aquatic environment is negligible and therefore it was considered not necessary to further address this issue.

The risk was assessed as low for bees, non-target organisms, earthworms, soil macro and micro-organisms, non-target plants and methods for sewage treatment for the representative use as seed treatment on winter cereals. The risk for the metabolite 1,2,4-triazole was considered low for birds and mammals, aquatic organisms and soil organisms.

6. Overview of the risk assessment of compounds listed in residue definitions for the environmental compartments

6.1. Soil

Compound (name and/or code)	Persistence	Ecotoxicology
bitertanol	Low to moderate persistence Single first order DT_{50} 4.0-20.4 days (20°C, pF2 soil moisture)	The risk for soil living organisms was assessed as low.
1,2,4-triazole	Low persistence[a] Single first order DT_{50} 5.0-9.9 days (20°C, pF2 soil moisture)	The risk for soil living organisms was assessed as low.

(a): Endpoints agreed at PRAPeR 12 meeting held on 15-18 January 2007

6.2. Ground water

Compound (name and/or code)	Mobility in soil	>0.1 µg/L 1m depth for the representative uses (at least one FOCUS scenario or relevant lysimeter)	Pesticidal activity	Toxicological relevance	Ecotoxicological activity
bitertanol	Low to slight mobility K_{Foc} 1766-37514 mL/g	no	yes	yes	yes
1,2,4-triazole	Very high to medium mobility K_{Foc} 43-202 mL/g	no	No data	yes	No

6.3. Surface water and sediment

Compound (name and/or code)	Ecotoxicology
bitertanol	Bitertanol is toxic to aquatic organisms. The lowest end point was observed in a chronic study on fish (NOEC: 0.0076 mg a.s./L). The risk was assessed as low.
1,2,4-triazole	The risk was assessed as low.

6.4. Air

Compound (name and/or code)	Toxicology
bitertanol	Low acute toxicity by inhalation (LC_{50} >1.254 mg/L).

LIST OF STUDIES TO BE GENERATED, STILL ONGOING OR AVAILABLE BUT NOT PEER REVIEWED

- Additional validation data on the confirmatory method for residues of bitertanol in treated plants (relevant for all representative uses evaluated; submission date proposed by the applicant: data already submitted, however according to Commission Regulation (EC) No. 33/2008, could not be considered in the peer review, see section 1)

- Monitoring method for air with a limit of quantification of 3 µg/m^3 (relevant for all representative uses evaluated; submission date proposed by the applicant: data already submitted, however according to Commission Regulation (EC) No. 33/2008, could not be considered in the peer review, see section 1)

- Bitertanol and its metabolites that retain 2 chiral centres consist of four isomers (2 diastereoisomer pairs). Information on the toxicity and/or on the degradation of the two enantiomers making up each diastereoisomer pair in animals, plants and the environment are not available. This information needs to be taken into account in the risk assessments when the patterns of use being assessed result in measurable residues or when predicted exposure levels are not negligibly low, (see sections 2, 3, 4 and 5)

- Assessment of the toxicological relevance of the impurities BUE 1662 and 3-chlorophenoxycompound, in order to demonstrate that the batches used in the toxicological studies are representative of the proposed technical specification (relevant for all representative uses evaluated; no submission date proposed by the applicant, some data already submitted in a position paper mentioned in the evaluation table, however according to Commission Regulation (EC) N° 33/2008, could not be considered in the peer review; see section 2)

- Data and information permitting the assessment of consumer exposure to triazole derivative metabolites (TDM) in primary crops and rotational crops, including their processed products, and products of animal origin (relevant for all representative uses evaluated; data gap identified by EFSA as outcome of the commenting period, no submission date proposed by the applicant; refer to section 3).

- Two seasons residues trials data in Southern Europe are required on cereals treated with bitertanol as a seed treatment (relevant for all representative uses evaluated; data gap identified by RMS as outcome of the commenting period, no submission date proposed by the applicant; refer to section 3).

- Information on the composition of the batches used in the ecotoxicology tests, including an assessment of the biological activity of the two diastereoisomers is required (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see section 5).

- Further data are required on the acute and short-term risk to granivorous birds to address the uncertainties associated with the existing dataset. (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see section 5)

- Data are required on the long-term/reproductive risk to birds in order to address the breeding potential in autumn. (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see section 5)

- Further data are required on the long-term risk to mammals. (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see section 5)

PARTICULAR CONDITIONS PROPOSED TO BE TAKEN INTO ACCOUNT TO MANAGE THE RISK(S) IDENTIFIED

- Appropriate protective equipment for the operators and workers (including respiratory protective equipment for the workers) is needed during seed treatment and handling of treated seed (see section 2).

ISSUES THAT COULD NOT BE FINALISED

- The plant residue definition for risk assessment is not finalised. Insufficient data is available to conduct a human and animal intake risk assessment for residues of triazole derivative metabolites resulting from the notified use of bitertanol in cereals. The contribution of the TDM residues present in primary and rotational crops, including their processed products, and in products of animal origin to the overall consumer exposure was not considered.

- The long-term risk to birds could not be finalised.

CRITICAL AREAS OF CONCERN

- The batches used for the toxicological studies were not demonstrated to be representative of the technical specification, due to the presence of two impurities of unknown toxicological relevance at higher levels in the technical specification.

- A high acute and short-term risk to birds was identified. The dataset provided was considered not sufficient to demonstrate a low risk.

- A high long-term risk to mammals was identified. The dataset provided was considered not sufficient to demonstrate a low risk.

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EFSA (2007). Scientific Opinion of the Panel on Plant Protection Products and their Residues on a request from EFSA related to the default *Q*10 value used to describe the temperature effect on transformation rates of pesticides in soil. The EFSA Journal (2007) 622, 1-32

[14] For further guidance documents see http://ec.europa.eu/food/plant/protection/resources/publications_en.htm#council (EC) or http://www.oecd.org/document/59/0,3343,en_2649_34383_1916347_1_1_1_1,00.html (OECD)

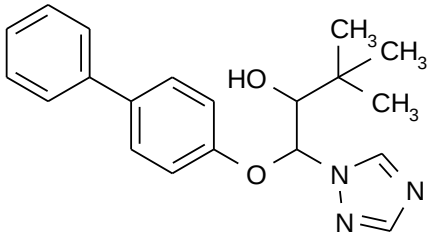
APPENDICES

APPENDIX A – LIST OF END POINTS FOR THE ACTIVE SUBSTANCE AND THE REPRESENTATIVE FORMULATION

Chapter 2.1 Identity, Physical and Chemical Properties, Details of Uses, Further Information

Active substance (ISO Common Name) ‡	Bitertanol
Function (*e.g.* fungicide)	fungicide
Rapporteur Member State	UK

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	(1*RS*,2*RS*;1*RS*,2*SR*)-1-(biphenyl-4-yloxy)-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl)butan-2-ol (20:80 ratio of (1*RS*,2*RS*)- and (1*RS*,2*SR*)-isomers).
Chemical name (CA) ‡	β-([1,1′-biphenyl]-4-yloxy)-α-(1,1-dimethylethyl)-1*H*-1,2,4-triazole-1-ethanol, [unstated stereochemistry]-
CIPAC No ‡	386
CAS No ‡	55179-31-2
EC No (EINECS or ELINCS) ‡	259-513-5
FAO Specification (including year of publication) ‡	AGP: CP/361 (1998) ≥ 900 g/kg RS+SR 70– 85% RR+SS 15– 30%
Minimum purity of the active substance as manufactured ‡	≥ 970 g/kg (A≥80, B≤20) RS+SR 80– 90% RR+SS 10– 20%
Identity of relevant impurities (of toxicological, ecotoxicological and/or environmental concern) in the active substance as manufactured	Open
Molecular formula ‡	$C_{20}H_{23}N_3O_2$
Molecular mass ‡	337.4
Structural formula ‡	

Physical and chemical properties (Annex IIA, point 2)

Melting point (state purity) ‡	118 °C (Eutectic mix)
Boiling point (state purity) ‡	Not measured, decomposes above 300°C
Temperature of decomposition (state purity)	>300 °C (98.7)
Appearance (state purity) ‡	White solid (pure – 96.7%) White greyish solid (technical)
Vapour pressure (state temperature, state purity) ‡	Diastereoisomer A = 2.2 x 10^{-10} Pa at 20°C (99.4%) Diastereoisomer B = 2.5 x 10^{-9} Pa at 20°C (97.4%)
Henry's law constant ‡	Diastereoisomer A = 2 x 10^{-8} Pa m^3/mol at 20°C Diastereoisomer B = 5 x 10^{-7} Pa m^3/mol at 20°C
Solubility in water (state temperature, state purity and pH) ‡	0.0038 g/l (Diastereoisomer A and B) at an unspecified pH and 20°C (solubility was stated to be unaffected by pH) (96.7%)
	Diastereoisomer A: 0.0027 g/l at 20 °C Diastereoisomer B: 0.0011 g/l at 20 °C
Solubility in organic solvents ‡ (state temperature, state purity)	<u>Diastereoisomer A+B</u> n-heptane 0.44g/l at 20°C (96.7%) xylene 18 g/l at 20°C (96.7%) dichloromethane >250g/l at 20°C (96.7%) 2-propanol 67g/l at 20°C (96.7%) 1-octanol 53g/l at 20°C (96.7%) polyethylene glycol 120g/l at 20°C (96.7%) acetone 200g/l at 20°C (96.7%) ethyl acetate 150g/l at 20°C (96.7%) acetonitrile 79g/l at 20°C (96.7%) dimethlsulfoxide >250g/l at 20°C (96.7%)
Surface tension ‡ (state concentration and temperature, state purity)	64 mN/m at 20 °C (96.7%)
Partition co-efficient ‡ (state temperature, pH and purity)	Diastereoisomer A - Log P_{OW} = 4.04 at 20°C (96.7%) Diastereoisomer B - Log P_{OW} = 4.15 at 20°C (96.7%)
Dissociation constant (state purity) ‡	No dissociation
UV/VIS absorption (max.) incl. ε ‡ (state purity, pH)	Diastereoisomer A = UV absorb 255 nm (ε=22059 l mol^{-1} cm^{-1}) (96.7%). No UV absorbance above 290 nm. Diastereoisomer B = UV absorb 255 nm (ε=21097 l mol^{-1} cm^{-1}) (96.7%). No UV absorbance above 290 nm.

Flammability ‡ (state purity)	Non-flammable (98.9%)
Explosive properties ‡ (state purity)	Non-explosive (98.9%)
Oxidising properties ‡ (state purity)	Non-oxidising (98.9%)

Summary of representative uses evaluated (bitertanol)*

Crop and/ or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks (m)
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	% product min max (n)	water L/ha min max	kg as/ha min max		
Winter wheat, winter barley, rye, triticale	EU North	Sibutol	F	a range of fungal pathogens	FS	398 g/L (375 + 23)	seed treat-ment	pre sowing	1	not applicable (0)	-	150 ml product / dt seed	56.25 g as / dt seed*	n.a.	* = 130 g as / ha at 230 kg seed / ha [1][2][3]
Winter wheat, winter barley, rye, triticale	EU South	Sibutol	F	a range of fungal pathogens	FS	398 g/L (375 + 23)	seed treat-ment	pre sowing	1	not applicable (0)	-	150 ml product / dt seed	56.25 g as / dt seed*	n.a.	* = 130 g as / ha at 230 kg seed / ha [1][2][3]

[1] A high acute and short term risk to birds was identified and the long-term risk was not finalised. A high long-term risk to mammals was identified.
[2] The batches used for the toxicological studies were not demonstrated to be representative of the technical specification.
[3] Consumer risk assessment not finalised due to data gaps in terms of relevant metabolites (TDM)

Remarks: ***(a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (e.g. fumigation of a structure)***

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

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

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

(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989

(f) All abbreviations used must be explained

(g) Method, e.g. high volume spraying, Low volume spraying, spreading, dusting, drench

(h) Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated

(i) g/kg or g/L

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

(k) The minimum and maximum number of application possible under practical conditions of use must be provided

(L) PHI - minimum pre-harvest interval

(m) Remarks may include: Extent of use/economic importance/restrictions

(n) product concentration of spray liquid

Chapter 2.2 Methods of Analysis

Analytical methods for the active substance (Annex IIA, point 4.1)

Technical as (analytical technique)	Bitertanol was determined in the technical active substance by GC-FID.
Impurities in technical as (analytical technique)	Organic impurities in technical material were determined by GC-FID Water content was determined by Karl Fischer titration
Plant protection product (analytical technique)	Bitertanol in the plant protection product was determined by GC-FID.

Analytical methods for residues (Annex IIA, point 4.2)

Residue definitions for monitoring purposes

Food of plant origin		Bitertanol
Food of animal origin		Bitertanol
Soil		Bitertanol
Water	surface	Bitertanol
	drinking/ground	Bitertanol
Air		Bitertanol

Monitoring/Enforcement methods

Food/feed of plant origin (analytical technique and LOQ for methods for monitoring purposes)	Bitertanol residues in plant and plant products were determined by S19 (GC-MS). The limit of determination was 0.02 mg/kg for grape, red currant and peanut and 0.05 mg/kg for wheat grain. Additional validation required for the confirmatory method.
Food/feed of animal origin (analytical technique and LOQ for methods for monitoring purposes)	Bitertanol residues in animal products were determined by S19 (GC-MS). The limit of determination was 0.01 mg/kg for milk, eggs and meat and 0.05 mg/kg for fat (data on liver and kidney were not requested as positive residues are unlikely to occur in animal products). The confirmatory method was not fully validated but as no MRLs are proposed this is not identified as a data gap.
Soil (analytical technique and LOQ)	Bitertanol residues in soil were determined by S19 (GC-MS). The limit of determination was 0.01 mg/kg.

Water (analytical technique and LOQ)	Bitertanol residues in water were determined by direct injection into a LC-MS/MS. The limit of determination was 0.05 μg/l.
Air (analytical technique and LOQ)	Bitertanol residues in air were determined by drawing air through a XAD adsorption tube and extracting the tube with acetonitrile/water. The resulting extracts were analysed by HPLC, using fluorescence detection (excitation 254 nm, emission 322 nm). The limit of determination was 10 μg/m^3. Data gap for a method with LOQ 3 μg/m^3
Body fluids and tissues (analytical technique and LOQ)	In support of therapeutic and diagnostic regimes, no methods of analysis were submitted or required as bitertanol is not classified as toxic.

Chapter 2.3 Impact on Human and Animal Health

Absorption, distribution, excretion and metabolism (toxicokinetics) (Annex IIA, point 5.1)

Rate and extent of oral absorption ‡	Rapidly and extensively absorbed: 80% based on urinary and biliary excretion, within 24 hours.
Distribution ‡	Widespread (highest levels in the liver and kidneys, the organs of excretion).
Potential for accumulation ‡	Low based on residue levels in the tissues at 7 days (0.2-0.4%)
Rate and extent of excretion ‡	Rapidly excreted in faeces (major route of excretion). Approximately 70% was excreted in bile within 12 hours. Minor amounts in urine (approximately 3.5% at 12 hours)
Metabolism in animals ‡	Metabolic reactions included hydroxylations, methylation, oxidation and cleavage. Biotransformation of the parent compound was extensive (>90%) but only 38-46% of the radioactivity was identified or characterised.
Toxicologically relevant compounds ‡ (animals and plants)	Bitertanol; 1,2,4-triazole & triazole acetic acid
Toxicologically relevant compounds ‡ (environment)	Bitertanol

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral ‡	>5000 mg/kg bw	
Mouse LD_{50} oral ‡	4202 mg/kg bw	
Rat LD_{50} dermal ‡	>2000 mg/kg bw in both sexes.	
Rat LC_{50} inhalation ‡	>1.254 mg/l (maximum attainable concentration, 4 hour dust exposure, head only)	
Skin irritation ‡	Not irritant	
Eye irritation ‡	Slight irritant (no C&L needed)	
Skin sensitisation ‡	Negative (M&K)	

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect ‡	Rat: liver Dog: adrenals, liver,eye, skin, thymus	
Relevant oral NOAEL ‡	12 mg/kg bw/d (90-d rat) 1 mg/kg bw/d (90-d & 12- mo dog) 0.3 mg/kg bw/d (2-yr dog)	

Relevant dermal NOAEL ‡	250 mg/kg bw/d (21-d rabbit)	
Relevant inhalation NOAEL ‡	0.0633 mg/litre of air (21-d rat)	

Genotoxicity ‡ (Annex IIA, point 5.4)

	No *in vitro/in vivo* potential for genotoxicity

Long term toxicity and carcinogenicity (Annex IIA, point 5.5)

Target/critical effect ‡	Reduced body weight gain (rats & mice)and increased adrenal weight (rat); liver effects (mouse)	
Relevant NOAEL Relavant LOAEL‡	Rats: 4.9 mg/kg bw/d (2-yr) Mice: 25 mg/kg bw/d (2-yr)	
Carcinogenicity ‡	No evidence of carcinogenic activity in rats or mice.	

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction toxicity

Reproduction target / critical effect ‡	Maternal: reduced body weight gain Reproduction: reductions in litter size at birth . Offspring: reduced body weight gain during lactation, decreased pup viability.	
Relevant parental NOAEL ‡	2.0 mg/kg bw/d	
Relevant reproductive NOAEL ‡	10.0 mg/kg bw/d	
Relevant offspring NOAEL ‡	10.0 mg/kg bw/d	

Developmental toxicity

Developmental target / critical effect ‡	Maternal: reduced body weight gain (rat, rabbit); clinical signs, reduced food intake, abortions/resorptions (rabbit) Developmental: reduced foetal weight (rabbit), stunted foetuses (rat, rabbit), skeletal variations (rat), delayed ossifications (rat, rabbit) Teratogenic: cleft palates (rats, rabbits); malformations of ribs and vertebral column (rats); epignathus, hypo/aplasia of lung lobes, malformation of sternum bone (”pigeon chest”) (rabbits)	R61 Repr. Cat 2
Relevant maternal NOAEL ‡	Rat : 10 mg/kg bw/d	

	Rabbit : 30 mg/kg bw/d	
Relevant developmental NOAEL ‡	Rat : 10 mg/kg bw/d Rabbit : 30 mg/kg bw/d NOAEL for teratogenic effects: 30 mg/kg bw/d (rat & rabbit)	

Neurotoxicity (Annex IIA, point 5.7)

Acute neurotoxicity ‡	No data submitted – not required.	
Repeated neurotoxicity ‡	NOAEL 12 mg/kg bw/d (13-wk rat neurotoxicity) No evidence of neurotoxicity.	
Delayed neurotoxicity ‡	Bitertanol is not a member of a chemical class associated with delayed neurotoxicity. Since there is no evidence of changes in nervous tissues in the recent 3-month neurotoxicity study, no further data are required.	

Other toxicological studies (Annex IIA, point 5.8)

Mechanism studies ‡	Investigations into hepatic enzyme activities and liver toxicity: NOAEL: 30 mg/kg bw/d. Hepatic enzyme induction occurred in male and female rats and there was some evidence for sex differences. Investigations into the CNS effects of Bitertanol: A slight stimulating effect on the CNS in mice at dose levels ≥0.6 mg/kg bw. Investigations into spontaneous motor activity: No effect on the spontaneous motor activity of male mice at dose levels up to 100 ppm (17.4 mg/kg bw/day). Investigations into cataract formation: There were no cataract-inducing effects in cats at an analysed concentration of 27.1 (mg/m3). Investigations into the irritation and/or sensitisation of the skin or mucosa (especially in the head region): There were no signs of irritation/sensitisation on the visible mucosa of dogs after inhalation exposure to bitertanol at concentrations of 0.0288 mg/l and 0.047 mg/l.

Studies performed on metabolites or impurities ‡	Reference values for triazole derivative metabolites: - 1,2,4-triazole: ADI 0.02 mg/kg bw/d ARfD 0.06 mg/kg bw - triazole acetic acid: ADI and ARfD of 1,2,4-triazole were chosen due to the limited data base available - triazole alanine: ADI 0.1 mg/kg bw/d ARfD 0.1 mg/kg bw
Studies performed on impurity BUE 1662	DEREK - No Alerts Rat acute oral LD50 - >1750 mg/kg bw Rat acute dermal LD50 - >5000 mg/kg bw Rat acute inhalation LC50 - >0.51 mg/L (Maximum achievable conc.) Not irritating to skin or eyes. Ames test – negative +/- S9

Medical data ‡ (Annex IIA, point 5.9)

Worker monitoring data: No significant adverse health effects have been reported for worker engaged in the manufacture and formulation of bitertanol products.

Summary (Annex IIA, point 5.10)

	Value	Study	Safety factor
ADI ‡	0.003 mg/kg bw/d	2 year dog	100
AOEL ‡	0.01 mg/kg bw/d	13 week & 12 month dog	100
ARfD ‡	0.01 mg/kg bw	13 week dog initial findings	100

Dermal absorption ‡ (Annex IIIA, point 7.3)

Sibutol FS398	3%, concentrate 17% aqueous dilution 8% grain dust Based on *in vitro* human data.

Exposure scenarios (Annex IIIA, point 7.2)

Operator	The exposure assessment uses representative higher tier exposure data covering sites located in the UK, Germany and France. Using these data, levels of total systemic exposure are estimated to be within

	the AOEL (21% for workers bagging and 34% for combined mixing / calibration/cleaning tasks). These predicted exposures reflect a worker wearing a long sleeved jacket and long trousers for all tasks, protective gloves for all tasks except bagging and an impermeable coverall (e.g. Tyvek) in addition to their standard work clothing for the cleaning operation.
Workers	Predicted exposure for workers wearing suitable protective clothing (coverall) and suitable respiratory protective equipment (RPE)* when handling seed treated with 'Sibutol FS 398' and contaminated equipment is estimated to be 100% of the AOEL. *RPE to provide a minimum 90% protection
Bystanders	Predicted exposures for bystanders (being considered as fork lift truck drivers as a worst case) are within (70%) the AOEL.

Classification and proposed labelling with regard to toxicological data (Annex IIA, point 10)

RMS/peer review proposal
Bitertanol: T Toxic, Repro. Cat. 2 R61 May cause harm to the unborn child

Chapter 2.4 Residues

Metabolism in plants (Annex IIA, point 6.1 and 6.7, Annex IIIA, point 8.1 and 8.6)

Plant groups covered	Tomato, cotton, wheat, apple and peanut
Rotational crops	Kale, wheat, sugar beet and mustard
Metabolism in rotational crops similar to metabolism in primary crops?	Unable to conclude, a study with triazole label is required
Processed commodities	Apple and tomato
Residue pattern in processed commodities similar to residue pattern in raw commodities?	**Bitertanol:** Yes for bitertanol residues **TDM:** Unable to conclude for TDM residues (data gap)
Plant residue definition for monitoring	Bitertanol
Plant residue definition for risk assessment	1. Bitertanol 2. Sum of TA and TAA (provisional, subject to outcome of required studies to address TDM (processing, rotational crops); pending definition via a global EU approach concerning TDM
Conversion factor (monitoring to risk assessment)	To be determined following the outcome of TDM review

Metabolism in livestock (Annex IIA, point 6.2 and 6.7, Annex IIIA, point 8.1 and 8.6)

Animals covered	Cattle and hens
Time needed to reach a plateau concentration in milk and eggs	Milk – 2 days Egg – 4 days
Animal residue definition for monitoring	Not triggered for the representative use; no MRLs proposed.
Animal residue definition for risk assessment	**Bitertanol:** Not triggered for the representative use for residues of bitertanol (based on available data: Bitertanol and its metabolite p-hydroxy bitertanol expressed as bitertanol.) **TDM:** Unable to conclude livestock exposure and metabolism for TDM
Conversion factor (monitoring to risk assessment)	Not applicable
Metabolism in rat and ruminant similar (yes/no)	Unable to conclude for TDM No triazole label study and TDM metabolism study available for livestock (potential data gap)
Fat soluble residue:	Yes

Residues in succeeding crops (Annex IIA, point 6.6, Annex IIIA, point 8.5)

Bitertanol: Residues of bitertanol based on the rotational crop metabolism study are unlikely to exceed the limit of determination (0.05 mg/kg). **TDM:** A study with triazole label is required (data gap)

Stability of residues (Annex IIA, point 6 introduction, Annex IIIA, point 8 Introduction)

Bitertanol: Residues of bitertanol are stable for up to 12 months (during freezer storage) in wheat forage, wheat straw, dry beans, cherry (supported by apple and peach data) and podded green beans. For wheat grain residues of bitertanol are stable for up to 5 months. For animal products (liver, kidney, muscle and fat) residues of bitertanol are stable for up to 28 months during freezer storage. **TDM:** no data available

Residues from livestock feeding studies (Annex IIA, point 6.4, Annex IIIA, point 8.3)

Ruminant:	Poultry:	Pig:
Conditions of requirement of feeding studies		
Bitertanol : No **TDM :** unable to conclude (data gap)	**Bitertanol :** No **TDM :** unable to conclude (data gap)	**Bitertanol :** No **TDM :** unable to conclude (data gap)

Summary of residues data according to the representative uses on raw agricultural commodities and feedingstuffs (Annex IIA, point 6.3, Annex IIIA, point 8.2)

Crop	Northern or Mediterranean Region, field or glasshouse, and any other useful information	Trials results relevant to the representative uses (a)	Recommendation/comments	MRL estimated from trials according to the representative use	HR (c)	STMR (b)
Cereal	N	**Bitertanol:** Grain: 18x<0.05 Straw: 18x<0.05 **TDM:** Data gap		0.05	0.05 open	0.05 open
	S	Data gap for residue trials in cereals				

(a) Numbers of trials in which particular residue levels were reported *e.g.* 3 x <0.01, 1 x 0.01, 6 x 0.02, 1 x 0.04, 1 x 0.08, 2 x 0.1, 2 x 0.15, 1 x 0.17
(b) Supervised Trials Median Residue *i.e.* the median residue level estimated on the basis of supervised trials relating to the representative use
(c) Highest residue

Consumer risk assessment (Annex IIA, point 6.9, Annex IIIA, point 8.8)

For Bitertanol:

ADI	0.003
TMDI (% ADI) – EFSA Model	Less than 20%
Total NEDI (% ADI) – UK Model	Less than 20%
ARfD	0.01
IESTI (% ARfD) – EFSA Model	Less than 8%
NESTI (% ARfD) – UK Model	Less than 8%

For TDM:

Significant consumer exposure to TA and TAA is expected from cereal grain. In addition, residues of TDM may possibly be present in rotational crops and food of animal origin. Although toxicological reference values are available for TDM, the consumer risk assessment is not finalised due to lack of data to estimate consumer exposure to TDM resulting from the representative use.

Processing factors (Annex IIA, point 6.5, Annex IIIA, point 8.4) for main metabolite BAM

Crop/ process/ processed product	Number of studies	Processing factors		Amount transferred (%) (Optional)
		Transfer factor (mean)*)	Yield factor	
Bitertanol:				
Apple Juice Wet pomace	1	 0.1 3		
Tomato Juice Preserve Paste	1	 0.1 0.4 2		
TDM:				
No data available for TDM residues (data gap)				

*) Individual results mentioned in brackets

Proposed MRLs (Annex IIA, point 6.7, Annex IIIA, point 8.6)

Bitertanol:	
Cereal grain	0.05* mg/kg

TDM: awaiting global EU approach concerning TDM

Chapter 2.5 Fate and Behaviour in the Environment

Route of degradation (aerobic) in soil (Annex IIA, point 7.1.1.1.1)

Mineralization after 100 days ‡	Parent bitertanol 43% AR after 91 days biphenyl label (n=1) 48-59% AR after 100 days phenyl label (n=4) 2.8% AR after 120 days triazole label (n=1) 1,2,4-triazole 1.6-52% AR after 90-120 days triazole label (n=6) 1,2,4-triazole acetic acid 1.96 – 6.23 % AR after 70 days (n=3)
Non-extractable residues after 100 days ‡	Parent bitertanol 46% AR after 91 days biphenyl label (n=1) 25-43% AR after 100 days phenyl label (n=4) 53% AR after 120 days triazole label (n=1) 1,2,4-triazole 38-67% AR after 90-120 days triazole label (n=6) 1,2,4-triazole acetic acid 34.71 – 43.16 % AR after 70 days (n=3)
Metabolites requiring further consideration ‡ - name and/or code, % of applied (range and maximum)	Major metabolite (>10%AR) 1,2,4-triazole 44% at 62 d (n=1) declining to 36% at study end (120 days) No other aerobic soil metabolites trigger assessment

Route of degradation in soil - Supplemental studies (Annex IIA, point 7.1.1.1.2)

Anaerobic degradation ‡

Mineralization after 100 days	Parent bitertanol Mineralisation ca. 3%AR after 60 d biphenyl label (n=1) 1,2,4-triazole Mineralisation 1.3% after 126 d triazole label (n=1)
Non-extractable residues after 100 days	Parent bitertanol Non extractable residues increased from ca. 34-38%AR over 60 days under anaerobic conditions, biphenyl label (n=1) 1,2,4-triazole Non extractable residues max 21% 64 days declining to 16% at study end 126d triazole label (n=1)
Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	Parent bitertanol None 1,2,4-triazole Major metabolite Triazole acetic acid 50% at study end 126 days triazole label (n=1)

Soil photolysis ‡	
Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	Parent bitertanol Stable to photolysis at the soil surface, thus not metabolites to consider.

Rate of degradation in soil (Annex IIA, point 7.1.1.2, Annex IIIA, point 9.1.1)

Laboratory studies ‡

Parent	Aerobic conditions						
Soil type		pH ($CaCl_2$)	t. °C / % MWHC	DT_{50} /DT_{90} (d)	DT_{50} (d) 20 °C pF2/10kPa	St. (χ^2)	Method of calculation
Sand		5.8	20 / 40-50	10.7	9.7	11.3	SFO
Loamy sand		6.3	20 / 40-50	20.4[1]	20.4	10.1	FOMC
Silt loam		7.3	20 / 40-50	6.4	4.3	8.1	SFO
Silt		7.2	20 / 40-50	4.2	4.0	11.5	SFO
Silt		6.7	20 / 50	12.6	12.6	4.6	SFO
Geometric mean					**8.8**[2]		

[1] Back calculated from FOMC DT90/3.32, actual FOMC DT50/DT90 8.1 days/67.7 days
[2] Overall geometric mean includes the geometric mean of the two silt soils (7.1 days)

1,2,4-triazole[1]	Aerobic conditions							
Soil type	X[1]	pH	t. °C / % MWHC	DT_{50}/ DT_{90} (d)	f. f. k_{dp}/k_f	DT_{50} (d) 20 °C pF2/10kPa	St. (r^2)	Method of calculation
Sandy loam		6.4	20°C / 40 % MWHC	6.32 / 21.0		5.0	0.75	SFO
Loamy sand		5.8	20°C / 40 % MWHC	9.91 / 33.0		9.9	0.81	SFO
Silt loam		6.7	20°C / 40 % MWHC	12.27 / 40.8		8.2	0.95	SFO
Geometric mean						7.4		

[1] 1,2,4-triazole endpoints agreed at PRAPeR 12 meeting

Triazole acetic acid	Aerobic conditions							
Soil type	X[1]	pH	t. °C / % MWHC	DT_{50}/ DT_{90} (d)	f. f. k_{dp}/k_f	DT_{50} (d) 20 °C pF2/10kPa	St. (r^2)	Method of calculation
Sand		5.2	20°C / 60 % MWHC	6.1 / 20.4		6.1	0.825	SFO
Loamy sand		5.6	20°C / 60 % MWHC	7.2 / 24.1		7.2	0.900	SFO
Sandy loam		6.3	20°C / 60 % MWHC	11.1 / 36.9		11.1	0.765	SFO
Geometric mean						7.9		

Field studies ‡ No studies submitted as not triggered by laboratory kinetics

pH dependence ‡ (yes / no) (if yes type of dependence)	No evidence of pH dependence
Soil accumulation and plateau concentration ‡	Not applicable

Laboratory studies ‡

Parent	Anaerobic conditions: Evidence from 3 data points indicate that over 60 d degradation was minimal (n=1)

Met 1,2,4-triazole	Anaerobic conditions							
Soil type	X[1]	pH (KCl)	t. °C / % MWHC	DT_{50}/ DT_{90} (d)	f. f. k_{dp}/k_f	DT_{50} (d) 20°C pF2/10kPa	St. (r^2)	Method of calculation
Silt loam		7.3	20	58			0.77	SFO

Soil adsorption/desorption (Annex IIA, point 7.1.2)

Parent ‡							
Soil Type	OC %	Soil pH ($CaCl_2$)	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Loam	1.58	5.5			35.8	2266	0.791
Silty clay	1.11	6.7			19.6	1766	0.883
Sand	1.95	6.9			39.9	2046	0.957
Loamy sand	1.99	5.4			49.27	2476	0.826
Sandy loam	1.02	6.3			38.26	3751	0.838
Arithmetic mean						2461	0.86
pH dependence, Yes or No			No evidence of pH dependence				

Metabolite 1,2,4-triazole[1] ‡							
Soil Type	OC %	Soil pH	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Silty clay	0.70	8.8			0.833	120	0.897
Clay loam	1.74	6.9			0.748	43	0.827
Sand	0.12	4.8			0.234	202	0.885[1]
Silty clay loam	0.70	7.0			0.722	104	0.922
Sandy loam	0.81	6.9			0.720	89	1.016
Arithmetic mean (of 4 values excluding the very low OC sand that was considered not representative of agricultural soils)					0.756	89	0.9155
pH dependence (yes or no)			No				

[1] Agreed end points for 1,2,4-triazole taken from PRAPeR 12 meeting

Mobility in soil (Annex IIA, point 7.1.3, Annex IIIA, point 9.1.2)

Column leaching ‡	No data submitted, none required
Aged residues leaching ‡	No data submitted, none required
Lysimeter/ field leaching studies ‡	No data submitted, none required

PEC (soil) (Annex IIIA, point 9.1.3)

Parent Method of calculation	DT_{50} (d): 20.4 days Kinetics: SFO Field or Lab: representative worst case from lab studies.
Application data	Crop: winter wheat Depth of soil layer: 5cm Soil bulk density: 1.5g/cm^3 % plant interception: Pre-emergence therefore no crop interception Number of applications: 1 Interval (d): not applicable Application rate(s): 130 g a.s./ha

$PEC_{(s)}$ (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial	0.173		Not applicable	
Short term 24h	0.168	0.170		
2d	0.162	0.168		
4d	0.151	0.162		
Long term 7d	0.137	0.154		
14d	0.108	0.138		
21d	0.085	0.124		
28d	0.067	0.112		
50d	0.032	0.083		
100d	0.006	0.049		
Plateau concentration	Not applicable			

Metabolite 1,2,4-triazole Method of calculation	Molecular weight relative to the parent: 69/337 DT_{50} (d): Not used, only initial PECsoil calculated Kinetics: Not used, only initial PECsoil calculated Field or Lab: Not used, only initial PECsoil calculated.
Application data	Application rate assumed: 130 g a.s./ha (assumed 1,2,4-triazole is formed at a maximum of 44 % of the applied dose)

$PEC_{(s)}$ (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial	0.016			
Short term 24h				
2d				
4d				
Long term 7d				
28d				
50d				
100d				
Plateau concentration	Not applicable			

Route and rate of degradation in water (Annex IIA, point 7.2.1)

Hydrolytic degradation of the active substance and metabolites > 10 % ‡	pH_:4 parent bitertanol stable to hydrolysis at 25&40ºC pH_:5 1,2,4 triazole stable to hydrolysis at 25ºC
	pH_:7 parent bitertanol stable to hydrolysis at 25&40ºC 1,2,4 triazole stable to hydrolysis at 25ºC
	pH_:9 parent bitertanol stable to hydrolysis at 25&40ºC 1,2,4 triazole stable to hydrolysis at 25ºC
Photolytic degradation of active substance and metabolites above 10 % ‡	Parent bitertanol 38ºN June days 9-20 mm light path length first order DT50 18 days sterile, 11 days natural water metabolites formed (phenyl label, sterile system) M04 max 24% AR at 6 test system d M27 38% AR at study termination (10 test system d) M28 16% AR at study termination. metabolites formed (triazole label, natural water) 1,2,4-triazole max 86% AR at 6 test system days
Quantum yield of direct phototransformation in water at Σ > 290 nm	0.0697 (units not specified)
Readily biodegradable ‡ (yes/no)	No data submitted, substance considered not ready biodegradable.

Degradation in water / sediment

Bitertanol	Distribution (max in water 31.3 – 37.4% 2-3 hours after dosing. Max. sed 53.9 – 71.9 % after 25 d)									
Water / sediment system	pH water phase	pH sed	t. °C	DT_{50}-DT_{90} whole sys.	St. (χ^2)	DT_{50}-DT_{90} water	St. (χ^2)	DT_{50}-DT_{90} sed	St. (χ^2)	Method of calculation
IJzendoorn silt loam	Not stated	7.7	22	45.7 / 151.8	18.8	8.5[1] / 28.3	3.7	41.0 / 136.1[2]	21.4	SFO (FOMC for water)
Lienden sandy loam	Not stated	8.1	22	32.4 / 107.7	11.9	18.6 / 61.7	11.8	24.4 / 81.0[2]	13.9	SFO
Geometric mean DT50				38.5		12.6		31.6		

[1] Calculated from FOMC DT90, i.e. DT90/3.32. Actual FOMC DT50 4.4 days

[2] Sediment values do not represent true dissipation from the peak observed concentration. An appropriate sediment dissipation value may need to be calculated separately if this required for MS assessments

Metabolite 1	No major metabolites formed in phenyl labelled water sediment studies (max unassigned radioactivity was at 4%AR in sediment). 1,2,4-triazole formation assumed to be 86% in FOCUS modelling (triazole-labelled water/sediment study not available)				
Mineralization and non extractable residues					
Water / sediment system	pH water phase	pH sed	Mineralization x % after n d. (end of the study).	Non-extractable residues in sed. max x % after n d	Non-extractable residues in sed. max x % after n d (end of the study)
IJzendoorn silt loam	Not stated	7.7	46.8% at 120 days	39.8% at 82 days	37.3% at 120 days
Lienden sandy loam	Not stated	8.1	49.0% at 120 days	33.0% at 120 days	33.0% at 120 days

PEC (surface water) and PEC sediment (Annex IIIA, point 9.2.3)

Parent Bitertanol Parameters used in FOCUSsw step 2 (Step 1 not available)	Version control no. of FOCUS calculator: Step 1-2, v 1.1 Molecular weight (g/mol): 337.4 Water solubility (mg/L): 3.8 K_{OC} (L/kg): 2461 DT_{50} soil (d): 8.1 days (Lab SFO)[1] DT_{50} water/sediment system (d): 39.1 (arithmetic mean of whole system DT50s from sediment/water studies)[2] DT_{50} water (d): whole system DT50 used DT_{50} sediment (d): whole system DT50 used Crop interception (%): 0
Parameters used in FOCUSsw step 3	Version control no.'s of FOCUS software: SWASH 2.1, MACRO 4.4.2, PRZM 3.21b, TOXSWA 2.1.2-F2 Vapour pressure: 6.76 x 10^{-10} Pa Kom/Koc: 1427.49 / 2461 1/n: 0.86 (Freundlich exponent general) Q10 2.58 Walker equation coefficient 0.7
Application rate	Crop: winter cereals (seed treatment) Crop interception: 0% Number of applications: 1 Interval (d): not applicable Application rate(s): 130 g as/ha Application window: Step 2, N & S Europe, Oct – Feb. Step 3, see below

[1] Soil DT50 of 8.1 days represents geomean of un-normalised DT50 values from Notifier calculations (included the SFO DT50 from BBA 2.2. soil rather that the FOMC DT90/3.32 in kinetic assessment study). RMS choice of normalised geomean DT50 is 8.8 days. However, this difference is not expected to significantly affect PECsw values.

[2] In light of FOCUS Kinetics guidance and EFSA (2007), it is considered that FOCUSsw Step 3 modelling for bitertanol should have used a water phase DT50 of 1000 days and sediment DT50 of 46.2 days (geomean of 38.5 days normalised form 22 to 20ºC using the activation energy of 65.4 kJ/mol equivalent to the Q10 of 2.58). In this case, impact of these parameters is expected to be negligible.

	Winter cereals	Application Window	
Scenario	Leaf emergence	Start (Julian days)	End (Julian days)
D1 Lanna	25th Sep.	26th Aug. (238)	25th Sep. (268)
D2 Brimstone	25th Oct.	25th Sep. (268)	25th Oct. (298)
D3 Vredepeel	21st Nov.	22nd Oct. (295)	21st Nov. (325)
D4 Skousbo	22nd Sep.	23rd Aug. (235)	22nd Sep. (265)
D5 La Jaillière	10th Nov.	11th Oct. (284)	10th Nov. (314)
D6 Thiva	30th Nov.	31st Oct. (304)	30th Nov. (334)
R1 Weiherbach	12th Nov.	13th Oct. (286)	12th Nov. (316)
R3 Bologna	1st Dec.	1st Nov. (305)	1st Dec. (335)
R4 Roujan	10th Nov.	11th Oct. (284)	10th Nov. (314)

Step 2 Bitertanol

		Northern Europe				Southern Europe			
	Time [days]	PEC_{sw} [µg/L]	TWA_{sw} [µg/L]	PEC_{sed} [µg/kg]	TWA_{sed} [µg/kg]	PEC_{sw} [µg/L]	TWA_{sw} [µg/L]	PEC_{sed} [µg/kg]	TWA_{sed} [µg/kg]
initial	0	3.59	-	88.44	-	2.88	-	70.76	-
short-term	1	3.53	3.56	86.89	87.67	2.82	2.85	69.51	70.13
	2	3.47	3.53	85.36	86.90	2.77	2.83	68.29	69.52
	4	3.35	3.47	82.39	85.38	2.68	2.78	65.91	68.31
long-term	7	3.17	3.38	78.12	83.18	2.54	2.70	62.50	66.54
	14	2.80	3.18	69.01	78.33	2.24	2.55	55.20	62.66
	21	2.48	3.00	60.95	73.85	1.98	2.40	48.76	59.08
	28	2.19	2.83	53.84	69.72	1.75	2.27	43.07	55.77
	42	1.71	2.53	42.01	62.37	1.37	2.03	33.61	49.90
	50	1.48	2.38	36.45	58.66	1.18	1.91	29.16	46.93
	100	0.61	1.68	15.02	41.42	0.49	1.35	12.02	33.13

Step 3 Bitertanol

Scenario	Water body	application date	$PEC_{sw, max}$ [µg/L]	21 day-$TWA_{sw, max}$ [µg/L]	$PEC_{sed, max}$ [µg/kg]
D1	Ditch	28th August 1982	< 0.0005	< 0.0005	< 0.0005
D1	Stream	28th August 1982	< 0.0005	< 0.0005	< 0.0005
D2	Ditch	9th October 1986	< 0.0005	< 0.0005	< 0.0005
D2	Stream	9th October 1986	< 0.0005	< 0.0005	< 0.0005
D3	Ditch	5th November 1992	< 0.0005	< 0.0005	< 0.0005
D4	Pond	27th August 1985	< 0.0005	< 0.0005	< 0.0005
D4	Stream	27th August 1985	< 0.0005	< 0.0005	< 0.0005
D5	Pond	11th October 1978	< 0.0005	< 0.0005	< 0.0005
D5	Stream	11th October 1978	< 0.0005	< 0.0005	< 0.0005
D6	Ditch	31st October 1986	< 0.0005	< 0.0005	< 0.0005
R1	Pond	13th October 1978	< 0.0005	< 0.0005	< 0.0005
R1	Stream	13th October 1978	< 0.0005	< 0.0005	< 0.0005
R3	Stream	15th November 1980	< 0.0005	< 0.0005	< 0.0005
R4	Stream	18 th October 1979	< 0.0005	< 0.0005	< 0.0005

Metabolite 1,2,4-triazole Parameters used in FOCUSsw step 2	Molecular weight: 69.1 Water solubility (mg/L): 730000 Soil or water metabolite: both Koc (L/kg): 89 DT_{50} soil (d): 9.2 days (Lab SFO) DT_{50} water/sediment system (d): 999 (worst case 'default') DT_{50} water (d): default whole system DT50 used DT_{50} sediment (d): default whole system DT50 used Crop interception (%): 0 Maximum occurrence observed (% molar basis with respect to the parent) Water/sediment: 86%[1] Soil: 44%
Application rate	Crop: winter wheat (seed treatment) Number of applications: 1 Interval (d): 1 Application rate(s): 130 g a.s./ha Depth of water body: x cm Application window: N & S Europe, Oct – Feb.
Main routes of entry	Run-off/drainage

[1] 86% justified on the basis that 86% AR formation observed in an aqueous photolysis study on bitertanol using natural water. FOCUS guidance at Step 2 for metabolites is that this value should be the maximum *observed* in both water and sediment. RMS considers this value to be sufficiently precautionary.

Step 2 1,2,4-triazole

		Northern Europe				Southern Europe			
	Time [days]	PEC_{sw} [µg/L]	TWA_{sw} [µg/L]	PEC_{sed} [µg/kg]	TWA_{sed} [µg/kg]	PEC_{sw} [µg/L]	TWA_{sw} [µg/L]	PEC_{sed} [µg/kg]	TWA_{sed} [µg/kg]
initial	0	1.29	-	1.15	-	1.03	-	0.92	-
short-term	1	1.29	1.29	1.15	1.15	1.03	1.03	0.92	0.92
	2	1.29	1.29	1.15	1.15	1.03	1.03	0.92	0.92
	4	1.29	1.29	1.15	1.15	1.03	1.03	0.92	0.92
long-term	7	1.28	1.29	1.14	1.15	1.03	1.03	0.91	0.92
	14	1.28	1.29	1.14	1.14	1.02	1.03	0.91	0.91
	21	1.27	1.28	1.13	1.14	1.02	1.03	0.91	0.91
	28	1.27	1.28	1.13	1.14	1.01	1.02	0.90	0.91
	42	1.25	1.27	1.12	1.13	1.00	1.02	0.89	0.91
	50	1.25	1.27	1.11	1.13	1.00	1.02	0.89	0.90
	100	1.20	1.25	1.07	1.11	0.96	1.00	0.86	0.89

PEC (ground water) (Annex IIIA, point 9.2.1)	
Method of calculation and type of study (*e.g.* modelling, field leaching, lysimeter)	For FOCUS gw modelling, values used – Modelling using FOCUS PEARL v 3.3.3 and FOCUS PELMO v 3.3.2, with appropriate FOCUSgw scenarios, according to FOCUS guidance. Scenarios: Chateaudun, Hamburg, Jokioinen, Kremsmunster, Okehampton, Piacenza, Porto, Sevilla, Thiva. Crop: Winter cereals Substance properties, see below
Application rate	Application rate: 130 g/ha (seed treatment). No. of applications: 1 Time of application: see below

Substance properties

Input parameter	Unit	bitertanol	1,2,4-triazole
Physico-chemical parameters			
Molecular mass	$g.mol^{-1}$	337.4	69.1
Vapour pressure	mPa	$6.8x10^{-8}$ (6.76×10^{-10} Pa in PEARL)	- (0.22 Pa in PEARL)
Water solubility	$mg.l^{-1}$	3.8	- (730000 in PEARL)
Plant uptake factor		0.5	0.5
Degradation parameters			
Geometric mean Half-life	days	7.3	7.4
Formation fraction from parent	%	-	1.00 (i.e. all parent is degraded to metabolite)
Normalised for temperature	°C	20 with Q10 2.58 (65.4 kJ/mol for PEARL)	20 with Q10 2.58 (65.4 kJ/mol for PEARL)
Exponent for moisture in soil		0.7	0.7
Reference soil moisture content relative to field capacity	%	100	100
Sorption parameters			
Arithmetic mean K_{fOC}	$cm^3.g^{-1}$	2461 (Kom for PEARL 1427.49)	89 (Kom for PEARL 51.62)
Arithmetic mean Freundlich adsorption exponent (1/n)		0.86	0.92

Application timing

Scenario	*Emergence winter cereals*	*Selected application dates*	*Application depth (cm)*
Châteaudun	26th Oct	20th Oct	4
Hamburg	1st Nov	12th Oct	4
Jokioinen	20th Sep	10th Sep	4
Kremsmünster	5th Nov	25th Oct	4
Okehampton	17th Oct	7th Oct	4
Piacenza	1st Dec	25th Nov	4
Porto	30th Nov	15th Nov	4
Sevilla	30th Nov	15th Nov	4
Thiva	30th Nov	15th Nov	4

PEC(gw) - FOCUS modelling results (80th percentile annual average concentration at 1m)

	Scenario	Parent (µg/L)	Metabolite (µg/L)
			1,2,4-triazole
PEARL/PELMO Winter wheat (seed treatment)	Chateaudun	<0.0001	<0.0001
	Hamburg	<0.0001	<0.0001
	Jokioinen	<0.0001	<0.0001
	Kremsmunster	<0.0001	<0.0001
	Okehampton	<0.0001	<0.0001
	Piacenza	<0.0001	<0.0001
	Porto	<0.0001	<0.0001
	Sevilla	<0.0001	<0.0001
	Thiva	<0.0001	<0.0001

Fate and behaviour in air (Annex IIA, point 7.2.2, Annex III, point 9.3)

Direct photolysis in air ‡	Not studied - no data requested
Quantum yield of direct phototransformation	Φ=0.0697
Photochemical oxidative degradation in air ‡	Atkinson Rate constant for reaction with OH radicals: 155(±77)x10^{-12} cm3/molecule.s, assuming a tropospheric OH concentration of 5x10^{5} radicals /cm^{3} a tropospheric half life of 2.5 hours is calculated. Model used: PHOTO v 3.0
Volatilisation ‡	from plant surfaces: ‡ No volatilisation following a foliar spray to barley was measured over 24 hours
	from soil: ‡ No volatilisation following a spray to

	the soil surface was measured over 24 hours
Metabolites	None

PEC (air)

Method of calculation	Expert judgement, based on vapour pressure, dimensionless Henry's Law Constant and information on volatilisation from plants and soil.

$PEC_{(a)}$

Maximum concentration	negligible

Residues requiring further assessment

Environmental occurring metabolite requiring further assessment by other disciplines (toxicology and ecotoxicology) or for which a groundwater exposure assessment is triggered.	Soil: bitertanol and 1,2,4-triazole Surface Water: bitertanol and 1,2,4-triazole Sediment: bitertanol and 1,2,4-triazole Ground water: bitertanol and 1,2,4-triazole Air: bitertanol

Monitoring data, if available (Annex IIA, point 7.4)

Soil (indicate location and type of study)	Data not available
Surface water (indicate location and type of study)	Data not available
Ground water (indicate location and type of study)	Data not available
Air (indicate location and type of study)	Data not available

Points pertinent to the classification and proposed labelling with regard to fate and behaviour data

Candidate for R53

Chapter 2.6 Ecotoxicology

Effects on terrestrial vertebrates (Annex IIA, point 8.1, Annex IIIA, points 10.1 and 10.3)

Species	Test substance	Time scale	End point (mg/kg bw/day)	End point (mg/kg feed)
Birds ‡				
Mallard duck	a.s.	Acute	>2000	n.a.
Bobwhite quail	a.s.	Acute	776	n.a.
Acute endpoint based on Finney calculation for mixed product		Acute	774	n.a.
Mallard duck	a.s.	Short-term	>346.2	>5000
Bobwhite quail	a.s.	Short-term	>171.5[a]	>808
Mallard duck	1,2,4-triazole	Short-term	>1354	>5000
Bobwhite quail	1,2,4-triazole	Short-term	>1410	>5000
Bobwhite quail	a.s.	Long-term	0.8	10
Bobwhite quail	a.s.	Long-term	2.5	33
Mallard duck	a.s.	Long-term	1.75	20
Mammals ‡				
Rat	a.s.	Acute	>5000	n.a.
Rat	Formulation	Acute	5000	n.a.
Rat	a.s.	Long-term/ reproduction	10	100
Additional higher tier studies ‡				
Several higher tier studies have been submitted and considered. The key avian studies are ones on avoidance that indicate that depending upon the feeding pressure birds tend avoid treated seed; however once consumed the treated seed can lead to adverse symptoms including diarrhoea that sometimes lead to death. Ecological studies indicated that for the use being supported that the skylark, yellowhammer and chaffinch were suitable focal species. Data were also submitted on the diet of these birds as well as the proportion of time spent in the treated area. Finally, an effects field trial was submitted that assessed the potential impact on radio-tracked birds that were known to be foraging on fields freshly sown with treated seed. This trial did not indicate any adverse symptoms on those birds radio-tracked. As regards mammals various field studies were submitted along with a population study and associated modelling.				

a The selected dietary endpoint was a dose at which no mortality occurred during the first five days, mortality of 30% occurred in the following 3 days. The reason why this dose level was selected was due to food avoidance occurring at other doses, and hence derivation of a true LC50 based on daily dose was not possible.

Toxicity/exposure ratios for terrestrial vertebrates (Annex IIIA, points 10.1 and 10.3)

Cereal seed treatment, SMS and NMS maximum application rate is equivalent to 129.375 g a.s./ha.

Indicator species/Category[2]	Time scale	ETE	TER[1]	Annex VI Trigger[3]
Tier 1				
Seed eating birds	Acute	214	3.6	10
Seed eating birds	Short-term	214	0.8	10
Seed eating birds	Chronic	data gap	data gap	5
Earthworm-eating birds	Chronic	0.41	5.1	5
Fish-eating birds	Chronic	Negligible exposure	Low concern	5
Higher tier refinement (Seed eating birds): The refined risk assessment reported below was questioned during the peer review and a data gap was set to further address the risk and the uncertainties in the existing dataset.				
	Acute Yellowhammer	43.3	21	10
	Short-term Yellowhammer	43.3	>4.7	10
	Acute Chaffinch	21.0	58	10
	Short-term Chaffinch	21.0	>12.8	10
	Acute Skylark	78.7	11.3	10
	Short-term Skylark	78.7	>2.5	10
	Acute Wood pigeon	73.1	10.6	10
	Short-term Wood pigeon	73.1	>2.3	10
	Acute Wood pigeon	17.9	43	10
	Short-term Wood pigeon	17.9	>9.6	10
Tier 1				
Seed eating mammals	Acute (form)	381	>13.1	10
Seed eating mammals	Long-term	129	0.1	5
Earthworm-eating mammals	Chronic	0.5	20	5
Fish-eating mammals	Chronic	Negligible exposure	Low concern	5

Indicator species/Category[2]	Time scale	ETE	TER[1]	Annex VI Trigger[3]
Higher tier refinement (Seed eating mammals): The refined risk based on modelling population was not accepted during the peer review and a data gap was proposed to further address the long-term risk to mammals				

[1] PDs of 0.58, 0.32 and 0.42 for yellowhammer, chaffinch and skylark were used,
PTs of 0.35, 0.22, 1.0 and 0.245 were used for yellowhammer, chaffinch, skylark and wood pigeon respectively

Toxicity data for aquatic species (most sensitive species of each group) (Annex IIA, point 8.2, Annex IIIA, point 10.2)

Group	Test substance	Time-scale (Test type)	End point	Toxicity[1] (mg/L)
Laboratory tests ‡				
Fish				
Oncorhynchus mykiss	a.s.	96 hr (static)	Mortality, EC_{50}	2.14 (n)
Lepomis macrochirus	a.s.	96 hr (static)	Mortality, EC_{50}	3.54 (n)
Oncorhynchus mykiss	a.s.	60 day, flow through	NOEC	0.0076 (n)
Oncorhynchus mykiss	1,2,4-triazole	96 hr static	Mortality EC50	498
Aquatic invertebrate				
Daphnia magna	a.s.	48 h (static)	Mortality, EC_{50}	4.46 (n)
Daphnia magna	a.s.	21 d (static)	Reproduction, NOEC	0.15 (n)
Daphnia magna	1,2,4-triazole	48 h (static)	Mortality EC50	>100
Sediment dwelling organisms				
Chironomus riparius	a.s.	28 d (static – spiked water)	Emergence NOEC Development NOEC	0.56 (n) 5.6 (n)
Algae				
Scenedesmus subspicatus	a.s.	72 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	1.38 (n) 6.52 (n)
Pseudokirchneriella subcaptiata	1,2,4-triazole	96 h (static)	ErC50 Ecell densityC50 EbC50	>31 12 13
Microcosm or mesocosm tests				
None submitted, none required				

(n) = nominal

Toxicity/exposure ratios for the most sensitive aquatic organisms (Annex IIIA, point 10.2)

FOCUS Step 2

Cereal seed treatment, SMS and NMS maximum application rate is equivalent to 129.375 g a.s./ha.

Test substance	N/S	Organism	Toxicity end point (mg/L)	Time scale	PEC[1]	TER	Annex VI Trigger[4]
a.s.	NMS	Fish	2.14	Acute	0.00359	596	100
a.s.	NMS	Fish	0.0076	Chronic	0.00359	**2.1**	10
a.s.	NMS	Aquatic invertebrates	4.46	Acute	0.00359	1242	100
a.s.	NMS	Aquatic invertebrates	0.15	Chronic	0.00359	42	10
a.s.	NMS	Algae	1.38	Chronic	0.00359	384	10
a.s.	NMS	Sediment dwelling invertebrates	0.56	Chronic	0.00359*	156	10
1,2,4-triazole	NMS	Fish	498	Acute	0.00129	386046	100
1,2,4-triazole	NMS	Aquatic invertebrates	>100	Acute	0.00129	>77519	100
1,2,4-triazole	NMS	Algae	12	Chronic	0.00129	9302	10

* it should be noted that theoretically the PEC should be the global maximum total load PECsw from Step 2; however as can be seen from the Step 3 PEC below, the refined PEC is effectively zero, therefore the global maximum has not been calculated.
[1] maximum values have been used.

Test substance	N/S	Organism	Toxicity end point (mg/L)	Time scale	PEC[1]	TER	Annex VI Trigger[4]
a.s.	SMS	Fish	2.14	Acute	0.00288	743	100
a.s.	SMS	Fish	0.0076	Chronic	0.00288	**2.6**	10
a.s.	SMS	Aquatic invertebrates	4.46	Acute	0.00288	1549	100
a.s.	SMS	Aquatic invertebrates	0.15	Chronic	0.00288	52	10
a.s.	SMS	Algae	1.38	Chronic	0.00288	479	10
a.s.	SMS	Sediment dwelling invertebrates	0.56	Chronic	0.00288*	194	10
1,2,4-triazole	SMS	Fish	498	Acute	0.00103	483495	100
1,2,4-triazole	SMS	Aquatic invertebrates	>100	Acute	0.00103	>97087	100
1,2,4-triazole	SMS	Algae	12	Chronic	0.00103	11650	10

* it should be noted that theoretically the PEC should be the global maximum total load PECsw from Step 2; however as can be seen from the Step 3 PEC below, the refined PEC is effectively zero, therefore the global maximum has not been calculated.
[1] maximum values have been used.

Refined aquatic risk assessment using higher tier FOCUS modelling.

FOCUS Step 3

Cereal seed treatment, SMS and NMS maximum application rate is equivalent to 129.375 g a.s./ha.

Test substance	Scenario[1]	Water body type	Test organism	Time scale	Toxicity end point (mg/L)	PEC	TER	Annex VI trigger
a.s.	D1, D2, D3, D4, D5, D6, R1, R3 and R4	Ditch, pond, stream	Fish	Chronic	0.0076	<0.0005	>15.2	10
a.s.	D1, D2, D3, D4, D5, D6, R1, R3 and R4	Ditch, pond, stream	Sediment dwelling invertebrates	Chronic	0.56	<0.0005	>1120	10

[1] As the PEC for all scenarios and waterbodies are the same all have been presented together.

Bioconcentration		
	Active substance	1,2,4-triazole
$logP_{O/W}$	4.04 – 4.15	-1.0
Bioconcentration factor (BCF)[1] ‡	170	n.a.
Annex VI Trigger for the bioconcentration factor	100	n.a.
Clearance time (days) (CT_{50}) and (CT_{90})	96% of residues gone within 3 days	n.a.
Level and nature of residues (%) in organisms after the 14 day depuration phase	<96%	n.a.

Effects on honeybees (Annex IIA, point 8.3.1, Annex IIIA, point 10.4)

Test substance	Acute oral toxicity (LD_{50} µg/bee)	Acute contact toxicity (LD_{50} µg/bee)
a.s. ‡	>104.4 (a.s.)	>200 (a.s.)
Baycor SC500	>239.8 (form)	>200 (form)
Field or semi-field tests		
2None submit, none required.		

Hazard quotients for honey bees (Annex IIIA, point 10.4)

'Sibutol FS398' is a flowable concentrate containing 375 g bitertanol/l and 23 g fuberidazole/l. The maximum application rate is 129 g a.s./ha.

As proposed use is as seed treatment, hazard quotients are not considered appropriate.

Test substance	Route	Hazard quotient	Annex VI Trigger
a.s.	Contact	n.a.	50
a.s.	oral	n.a.	50
Preparation	Contact	n.a.	50
Preparation	oral	n.a.	50

Effects on other arthropod species (Annex IIA, point 8.3.2, Annex IIIA, point 10.5)

'Sibutol FS398' is a flowable concentrate containing 375 g bitertanol/l and 23 g fuberidazole/l. The maximum application rate is 129 g a.s./ha.

Laboratory studies

Laboratory tests with standard sensitive species

Species	Test Substance	End point	Effect (LR_{50} g a.s./ha)
Typhlodromus pyri ‡	Baycor SC500	Mortality	>6000
Aphidius rhopalosiphi ‡	Baycor SC500	Mortality	>1000

Species	Life stage	Test substance, substrate and duration	Dose (g/ha)	End point	% effect	Trigger value
Poecilus cupreus	adult	Sibutol FS398' Ext. Lab., 14 d, soil (Lufa 2.1), dressed seed bitertanol 200 g a.s./ha fuberidazole 11.4 g a.s./ha	200	Adult mortality, food consumption (14 days)	No mortality and no reduction in food consumption	50 %

Species	Life stage	Test substance, substrate and duration	Dose (g/ha)	End point	% effect	Trigger value
Pardosa spp (4 species)	mainly adults	Sibutol FS398' Ext. Lab., 14 d, soil (Lufa 2.1), dressed seed bitertanol 230 g a.s./ha fuberidazole 12.8 g a.s./ha	219	Mortality, food consumption (14 days)	Corrected mortality 6.1%. Reduction in food consumption 14.7%	50 %
Aleochara bileneata	Adults 1-3 days old	Sibutol FS398' Ext. Lab., 82 d, soil (Lufa 2.1), dressed seed bitertanol 204.5 g a.s./ha fuberidazole 11.6 g a.s./ha	204.5	Mortality, reproductive capacity (28 days)	16.6% in reproductive capacity	50 %

Field or semi-field tests
Indicate if not required

Effects on earthworms, other soil macro-organisms and soil micro-organisms (Annex IIA points 8.4 and 8.5. Annex IIIA, points, 10.6 and 10.7)

Test organism	Test substance	Time scale	End point
Earthworms			
	Bitertanol	Acute 14 days	LC_{50} >1000 mg a.s./kg d.w.soil; equivalent to >500 mg a.s./kg soil due to logPow>2
	Sibutol FS398	Acute	>1000 mg product/kg dry soil, as log pow is >2 this is equivalent to >500 mg product/kg soil; equivalent or 187.5 mg a.s./kg soil
	Baycor SC500	Chronic 8 weeks	NOEC 950 g product/ha, equivalent to 2.7 mg a.s./kg dry soil[a]
	Baycor FS398	Chronic 8 weeks	NOEC 460 kg treated seed[a]
	1,2,4-triazole	Acute	LC50>1000 mg/kg dry wt soil
	1,2,4-triazole	Chronic	NOEC 1 mg/kg dry wt soil
Other soil macro-organisms			
Collembola			
	Sibutol FS398	Chronic (28 days)	NOEC 140 mg product/kg d.w.soil, equivalent to 47 mg a.s./kg d soil or 23.5 mg a.s./kg d soil due to LogPow >2
	1,2,4-triazole	Chronic (28 days)	NOEC 1.8 mg/kg d.w.soil
Soil micro-organisms			
Nitrogen mineralisation	Sibutol SC500	28 days	At a doses of up 2.3l product/ha (equivalent to 0.86 kg bitertanol/ha) there was no significant effect on nitrogen mineralisation (<25% difference to untreated control) in 28-day study.
Nitrogen mineralisation	1,2,4-triazole	28 days	At doses of up to 0.35 mg/kg d w soil there was no significant effect on nitrogen mineralisation (<25% difference to untreated control) in 28-day study.

Test organism	Test substance	Time scale	End point
Carbon mineralisaton	Sibutol SC500	28 days	At doses of up 2.3l product/ha (equivalent to 0.86 kg bitertanol/ha) there was no significant effect on carbon mineralisation (<25% difference to untreated control) in 28-day study.
Carbon mineralisaton	1,2,4-triazole	28 days	At doses of up to 0.35 mg/kg d w soil there was no significant effect on carbon mineralisation (<25% difference to untreated control) in 28-day study.
Field studies			
None submitted or required			

[1] indicate where end point has been corrected due to log Pow >2.0 (e.g. LC_{50corr})
[2] litter bag, field arthropod studies not included at 8.3.2/10.5 above, and earthworm field studies
[a] two chronic earthworm studies were submitted, one used treated seed whilst the other involved treated (i.e. sprayed) soil. On the one hand the former study appears more realistic as it assesses the toxicity from the seed treatment there is the confounding issue of 'hotspots'. The density of these hotspots would be greater (due to higher drilling rates) and potentially unrealistic compared to the GAP. The risk assessment below has been done using both endpoints.

Toxicity/exposure ratios for soil organisms

Crop and application rate

Test organism	Test substance	Time scale	Soil PEC[2]	TER	Trigger
Earthworms					
	Sibutol FS398	Acute	0.173	>1084	10
	Baycor SC500	Chronic	0.173	15.6	5
	Baycor FS398	Chronic	230[a]	2.6	5
	1,2,4-triazole	Acute	0.016	>62500	10
		Chronic	0.016	62.5	5
Other soil macro-organisms					
Collembola	Sibutol FS398	Chronic	0.173	136	5
Collembola	1,2,4-triazole	Chronic	0.016	112.5	5

[1] to be completed where first Tier triggers are breached
[2] indicate which PEC soil was used (e.g. plateau PEC)
a The study used seed treated at 72 g/100 kg seed, whereas the proposed GAP is 56 g/100 kg seed. The study also used higher drilling densities. The NOEC from this study was equivalent to seed drilled at twice the maximum drilling rate (i.e. 460 kg seeds/ha compared to 230 kg seeds/ha) with seed treated at 1.3 times the proposed rate. The study gave a NOEC that was equivalent to 2.6 times the GAP, i.e. TER was 2.6.

Effects on non target plants (Annex IIA, point 8.6, Annex IIIA, point 10.8)

Laboratory dose response tests

Most sensitive species	Test substance	ER_{50} (g/ha) vegetative vigour	ER_{50} (g a.s./ha) emergence	Exposure[1] (g/ha)	TER	Trigger
Amaranthus retroflexus	Bitertanol as Baycor 500 SC	>6840 (35% effect at 6840 g a.s./ha)	>6840 (30% effect at 6840 g a.s./ha)	0	n.a.	5

[1] Proposed use is as a seed treatment, therefore exposure to non-target vegetation is considered to be zero.

Additional studies (e.g. semi-field or field studies)

None submitted or required

Effects on biological methods for sewage treatment (Annex IIA 8.7)

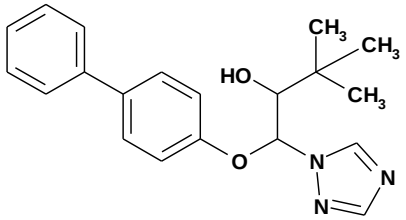
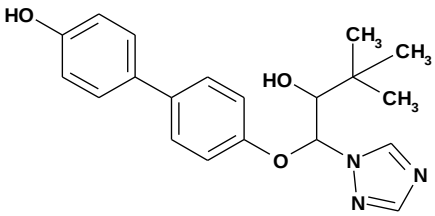
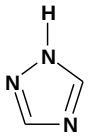
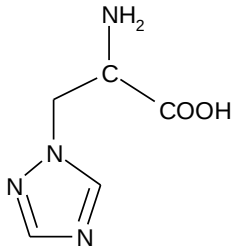
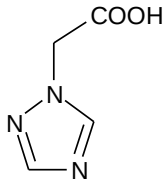
Test type/organism	end point
Activated sludge	EC50 > 10000 mg a.s./L

Ecotoxicologically relevant compounds (consider parent and all relevant metabolites requiring further assessment from the fate section)

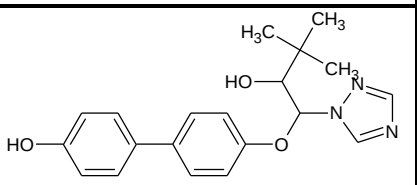
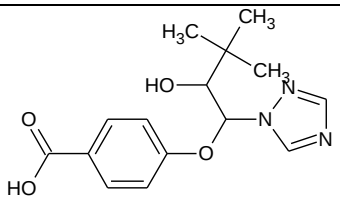
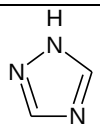
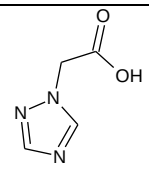
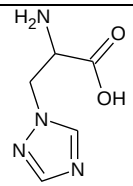
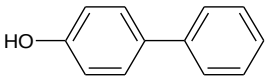
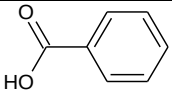
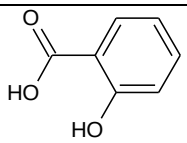
Compartment	
soil	Bitertanol
water	Bitertanol
sediment	Bitertanol
groundwater	None

Classification and proposed labelling with regard to ecotoxicological data (Annex IIA, point 10 and Annex IIIA, point 12.3)

Active substance	R51, R53, N
Preparation	R51, R53 N, S35 and S57

Code/Trivial name	Chemical name	Structural formula
Bitertanol KWG 0599 BAYCOR	Stoichiometric formula: $C_{20}H_{23}N_3O_2$ β-([1,1-biphenyl]-4-yloxy)-α-(1,1-dimethylethyl)-1*H*-1,2,4-triazole-1-ethanol (CAS) *[55179-31-2]*	
p-Hydroxy bitertanol CHE 10010 p-Hydroxy BAYCOR p-OH BAYCOR Mobay 729	Stoichiometric formula: C20 H23 N3 O3 α-(1,1-dimethylethyl)-β-[(4'-hydroxy[1,1'-biphenyl]-4-yl)oxy]-1H-1,2,4-triazole-1-ethanol (CAS)	
1, 2, 4-Triazole CGA 71019	Stoichiometric formula: $C_2H_3N_3$ 1*H*-1,2,4-triazole (CAS, IUPAC)	
Triazole alanine TA THS 2212 CGA 131013	Stoichiometric formula: $C_5H_8N_4O_2$ 3-(1*H*-1,2,4-triazol-1-yl)-alanine (CAS) 2-amino-3-(1*H*-1,2,4-triazol-1-yl)-propionic acid	
Triazole acetic acid TAA CGA 142856	Stoichiometric formula: $C_4H_5N_3O_2$ 1*H*-1,2,4-triazole-1-acetic acid (CAS) 1*H*-1,2,4-triazol-1yl-acetic acid	

APPENDIX B – USED COMPOUND CODE(S)

Code/Trivial name	Chemical name*	Structural formula*
p-hydroxy bitertanol	4'-{[(1*RS*,2*RS*;1*RS*,2*SR*)-2-hydroxy-3,3-dimethyl-1-(1*H*-1,2,4-triazol-1-yl)butyl]oxy}biphenyl-4-ol	
bitertanol-benzoic acid, M01	4-{[(1*RS*,2*RS*;1*RS*,2*SR*)-2-hydroxy-3,3-dimethyl-1-(1*H*-1,2,4-triazol-1-yl)butyl]oxy}benzoic acid	
1,2,4-triazole	1*H*-1,2,4-triazole	
triazole acetic acid M07 TAA	1*H*-1,2,4-triazol-1-ylacetic acid	
triazole alanine (TA)	3-(1*H*-1,2,4-triazol-1-yl)-DL-alanine	
4-hydroxy biphenyl M04	biphenyl-4-ol	
benzoic acid M27	benzoic acid	
salicylic acid M28	2-hydroxybenzoic acid	

* ACD/ChemSketch, Advanced Chemistry Development, Inc., ACD/Labs Release: 12.00 Product version: 12.00 (Build 29305, 25 Nov 2008).

ABBREVIATIONS

(Only highlighted entries will be kept in final conclusion)

(Please highlight additional entries in Turquoise)

1/n	slope of Freundlich isotherm
ε	decadic molar extinction coefficient
°C	degree Celsius (centigrade)
µg	microgram
µm	micrometer (micron)
a.s.	active substance
AChE	acetylcholinesterase
ADE	actual dermal exposure
ADI	acceptable daily intake
AF	assessment factor
AOEL	acceptable operator exposure level
AP	alkaline phosphatase
AR	applied radioactivity
ARfD	acute reference dose
AST	aspartate aminotransferase (SGOT)
AV	avoidance factor
BCF	bioconcentration factor
BUN	blood urea nitrogen
bw	body weight
CAS	Chemical Abstract Service
CFU	colony forming units
ChE	cholinesterase
CI	confidence interval
CIPAC	Collaborative International Pesticide Analytical Council Limited
CL	confidence limits
d	day
DAA	days after application
DAR	draft assessment report
DAT	days after treatment
DM	dry matter
DT_{50}	period required for 50 percent disappearance (define method of estimation)
DT_{90}	period required for 90 percent disappearance (define method of estimation)
dw	dry weight
EbC_{50}	effective concentration (biomass)
EC_{50}	effective concentration
ECHA	European Chemical Agency
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EMDI	estimated maximum daily intake
ER_{50}	emergence rate/effective rate, median
ErC_{50}	effective concentration (growth rate)
EU	European Union
EUROPOEM	European Predictive Operator Exposure Model
f(twa)	time weighted average factor
FAO	Food and Agriculture Organisation of the United Nations
FIR	Food intake rate
FOB	functional observation battery
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use

g	gram
GAP	good agricultural practice
GC	gas chromatography
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GGT	gamma glutamyl transferase
GM	geometric mean
GS	growth stage
GSH	glutathion
h	hour(s)
ha	hectare
Hb	haemoglobin
Hct	haematocrit
hL	hectolitre
HPLC	high pressure liquid chromatography or high performance liquid chromatography
HPLC-MS	high pressure liquid chromatography – mass spectrometry
HQ	hazard quotient
IEDI	international estimated daily intake
IESTI	international estimated short-term intake
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint Meeting on 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_{doc}	organic carbon linear adsorption coefficient
kg	kilogram
K_{Foc}	Freundlich organic carbon adsorption coefficient
L	litre
LC	liquid chromatography
LC_{50}	lethal concentration, median
LC-MS	liquid chromatography-mass spectrometry
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LD_{50}	lethal dose, median; dosis letalis media
LDD_{50}	lethal daily dose
LDH	lactate dehydrogenase
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification (determination)
m	metre
M/L	mixing and loading
MAF	multiple application factor
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
mg	milligram
mL	millilitre
mm	millimetre
MRL	maximum residue limit or level
MS	mass spectrometry
MSDS	material safety data sheet
MTD	maximum tolerated dose
MWHC	maximum water holding capacity
NESTI	national estimated short-term intake
ng	nanogram
NOAEC	no observed adverse effect concentration

NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
OM	organic matter content
Pa	Pascal
PD	proportion of different food types
PEC	predicted environmental concentration
PEC_{air}	predicted environmental concentration in air
PEC_{gw}	predicted environmental concentration in ground water
PEC_{sed}	predicted environmental concentration in sediment
PEC_{soil}	predicted environmental concentration in soil
PEC_{sw}	predicted environmental concentration in surface water
pH	pH-value
PHED	pesticide handler's exposure data
PHI	pre-harvest interval
PIE	potential inhalation exposure
pK_a	negative logarithm (to the base 10) of the dissociation constant
P_{ow}	partition coefficient between *n*-octanol and water
PPE	personal protective equipment
ppm	parts per million (10^{-6})
ppp	plant protection product
PT	proportion of diet obtained in the treated area
PTT	partial thromboplastin time
QSAR	quantitative structure-activity relationship
r^2	coefficient of determination
RPE	respiratory protective equipment
RUD	residue per unit dose
SC	suspension concentrate
SD	standard deviation
SFO	single first-order
SSD	species sensitivity distribution
STMR	supervised trials median residue
$t_{1/2}$	half-life (define method of estimation)
TDM	triazole derivative metabolites
TER	toxicity exposure ratio
TER_A	toxicity exposure ratio for acute exposure
TER_{LT}	toxicity exposure ratio following chronic exposure
TER_{ST}	toxicity exposure ratio following repeated exposure
TK	technical concentrate
TLV	threshold limit value
TMDI	theoretical maximum daily intake
TRR	total radioactive residue
TSH	thyroid stimulating hormone (thyrotropin)
TWA	time weighted average
UDS	unscheduled DNA synthesis
UV	ultraviolet
W/S	water/sediment
w/v	weight per volume
w/w	weight per weight
WBC	white blood cell
WG	water dispersible granule
WHO	World Health Organisation
wk	week
yr	year