Conclusion regarding the peer review of the pesticide risk assessment of the active substance

bromuconazole.

Finalised: 26 March 2008

SUMMARY

Bromuconazole is one of the 79 substances of the third stage Part A of the review programme covered by Commission Regulation (EC) No 1490/2002[1]. This Regulation requires the European Food Safety Authority (EFSA) to organise upon request of the EU-Commission a peer review of the initial evaluation, i.e. the draft assessment report (DAR), provided by the designated rapporteur Member State and to provide within one year a conclusion on the risk assessment to the EU-Commission.

Belgium being the designated rapporteur Member State submitted the DAR on bromuconazole in accordance with the provisions of Article 10(1) of the Regulation (EC) No 1490/2002, which was received by the EFSA on 14 November 2005. Following a quality check on the DAR, the peer review was initiated on 5 May 2006 by dispatching the DAR for consultation of the Member States and the sole applicant Bayer CropScience. Subsequently, the comments received on the DAR were examined by the rapporteur Member State and remaining issues were agreed during a written procedure in February – March 2007. The identified issues as well as further information made available by the applicant upon request were evaluated in a series of scientific meetings with Member State experts in July and October 2007.

A final discussion of the outcome of the consultation of experts took place during a written procedure with the Member States in February-March 2008 leading to the conclusions as laid down in this report.

The conclusion was reached on the basis of the evaluation of the representative uses as a fungicide on wheat full details of the gap can be found in the attached list of end points.
The representative formulated product for the evaluation was "EXP10064C", a suspension concentrate formulation (SC).

Adequate methods are available to monitor all compounds given in the respective residue definition. Residues in food of plant origin can be determined with a multi-method (The German S19 method

[1] OJ No L 224, 21.08.2002, p. 25 as last amended by Regulation (EC) No 1095/2007 (OJ L 246, 21.9.2007, p. 19)

has been validated). For the other matrices only single methods are available to determine residues of bromuconazole.
Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection product are possible. The remaining issues are that the technical specification can not be finalised and there is a data gap identified for a dissociation constant study.

In mammals, bromuconazole oral LD50 is 328 mg/kg bw (classification as "harmful if swallowed" (Xn; R22), proposed). The acute toxicity by dermal and inhalation route is low (LD50>2000 mg/kg bw and LC50>5 mg/L). Bromuconazole is neither skin nor eye irritant. It is not a skin sensitiser.
In repeated dose toxicity studies, the liver is the target organ. In subchronic tests, the dog is the most sensitive species, with an overall relevant NOAEL of 2.5 mg/kg bw/day whereas in rat the NOAEL is 13.8 mg/kg bw/day. In genotoxicity testing there was some indication of weak clastogenicity *in vitro*, however there was no indication of positive results were *in vivo*, neither in the micronucleus assay nor in the UDS assay. Overall, bromuconazole was considered devoid of genotoxic potential.
The relevant NOAEL for long term toxicity and carcinogenicity in rat is 0.88 mg/kg bw/day: treatment-related neoplastic lesions in rodents occurred at high doses: hepatocellular and cholangiocellular carcinomas in rats and hepatocellular carcinoma in mice. In both rats and mice, the tumours were likely caused by liver toxicity and subsequent cell renewal. Overall, it was agreed that bromuconazole does not have carcinogenic potential relevant to humans. Bromuconazole did not show any reproductive toxicity potential: parental and foetal toxicity NOAELs were established at 1.3 mg/kg bw/day, while the reproductive NOAEL was established at 141 mg/kg bw/day. As for developmental toxicity, in the rat the relevant maternal NOAEL is 70 mg/kg bw/day, whereas the developmental NOAEL is 10 mg/kg bw/day, based on a dose-dependent increase of placental weight and ossification delays or supernumerary bones in a number of skeletal structures. It was agreed to propose classification Cat 3, Xn; R63, 'May cause harm to unborn child'. The ADI of 0.01 mg/kg bw/day was set based on the relevant long term toxicity/carcinogenicity NOAEL of 0.88 mg/kg bw/day from the 2 year rat study, applying an SF of 100. For the ARfD, the value is based on the developmental NOAEL of 10 mg/kg bw/day from the rat study, with an SF of 100, leading to an ARfD of 0.1 mg/kg bw. The AOEL of 0.025 mg/kg bw/day was set on basis of the NOAEL of 2.5 mg/kg bw/day from the 90-day dog study (applying a standard SF of 100). The operator exposure showed exposure levels below the AOEL (15.6%) with the application of the German model and the use of gloves during mixing/loading and application and coveralls and sturdy footwear during application. The estimated exposure for re-entry activities (scouting) is 1.5% of the AOEL. The bystander exposure is estimated to be 1.6% of the AOEL.

The metabolism of bromuconazole was investigated in wheat (relevant to the notified use). Additional metabolism data was submitted for the category of fruit crops. A metabolic pathway could be established in cereals. At harvest, bromuconazole was still a major part of the terminal residue in cereal matrices and identified metabolites were individually below 10% of the total residue. However, there was indication of preferential metabolism of one bromuconazole diastereomer (LS 850647), as a

significant shift in the ratio of diastereomers was found in the residues determined in the mature cereal crop when compared to the ratio in the initially applied bromuconazole. Whether the ratio of enantiomers in each diastereomer was subject to any shift was not investigated.

In rotational crops studies there was uptake of residues from soil into succeeding cereal, oilseed, root and leafy crops. Upon analysis of the residues the two bromuconazole diastereomers were identified as major residue, and similar to the primary cereal metabolism their ratio had been shifted compared to the one in the bromuconazole applied to the soil. No information is available on the ratio of enantiomers in each diastereomer.

The submitted livestock metabolism data in ruminants and poultry allows to establish a metabolic pathway, and suggests that no residues in food of animal origin above the limit of quantification are expected when cereals treated according the cGAP are used in livestock diet. The data implies that there might be preferential metabolism of one diastereomers also in livestock animals. The ratio of enantiomers in each diastereomer was not investigated.

As plant and livestock residue data indicate that from the notified use no significant consumer exposure to bromuconazole residues is expected, the observed shift of the isomer ratio in the terminal residue is currently not a concern with regard to consumer safety. This may have to be reconsidered when authorisation of uses is sought that lead to consumer exposure to bromuconazole residues above the limit of quantification.

The meeting of experts noted that all studies were performed using phenyl-labelled bromuconazole only, and thus the fate of the triazole moiety of the molecule was not investigated. The experts agreed that based on the available data and information cleavage of the molecule cannot be excluded and further investigation of the triazole moiety is required to address potential consumer exposure to triazole derivative metabolites. Until then, the plant and animal residue definition is provisional, and consequently the consumer risk assessment is not finalised.

In soil under aerobic conditions bromuconazole exhibits high to very high persistence forming several minor (< 10% AR) metabolites. Mineralisation was limited accounting for only 1-4.4% AR after 100-120 days. The formation of unextractable residues was a sink, accounting for 5-17.6 % AR after 100-120 days. Laboratory soil photolysis study indicated that photolysis may contribute to the degradation of bromuconazole at the soil surface. As a consequence, the experts agreed that the available dissipation rates do not represent biodegradation that can be used as input to FOCUS modelling. Bromuconazole exhibits medium to low mobility in soil. Provisional PECsoil accumulation value was obtained from accumulation field studies. Bromuconazole is essentially stable to hydrolysis and photolysis is not expected to be a significant process in the breakdown of bromuconazole in natural aquatic systems. In dark natural sediment water systems bromuconazole partitioned from the water column to sediment where it exhibited very high persistence. The terminal metabolite, CO_2, accounted for a maximum of 0.9 % AR at 100 days (study end). Unextracted sediment residues were a sink but represented maximum 15% AR at study end.

Potential for contamination of surface water and groundwater cannot be adequately assessed because reliable degradation rates in soil under field conditions are not available.

The first-tier TER values for herbivorous birds were above the Annex VI trigger values indicating a low risk. Also the acute and short-term TERs for insectivorous birds were well above the trigger while the long-term TER of 4.4 indicated a potential high long-term risk. The RMS considered the long-term risk as addressed based on the argument that refinement of PT and PD would lead to a TER above the trigger of 5. However no further information/argumentation was provided to support a PT or PD refinement. The experts agreed that the risk needs to be addressed further and an open point was set for the RMS to conduct a refined long-term risk assessment for insectivorous birds. No new risk assessment was provided and a data gap is proposed by EFSA to address the long-term risk to insectivorous birds. The risk to mammals was assessed for small herbivorous mammals for the early application, and to insectivorous mammals for the late application. The acute TERs for herbivorous and insectivorous mammals were above the trigger of 10 (including refinement of residues in plant material). The choice of the long-term endpoint was discussed in the expert meeting. The experts considered effects on bodyweight and bodyweight gain observed at the dose of 13.8 mg a.s./kg bw/d as relevant and suggested to use the next lower dose of 1.3 mg a.s/kg bw/d as the NOAEL in the risk assessment. The updated risk assessment resulted in long-term TERs below the trigger of 5. Further refinement of the long-term risk to herbivorous, insectivorous and vermivorous mammals is necessary.

Bromuconazole is very toxic to aquatic organisms. A potential high risk was indicated in with FOCUS step3 PECsw values. The available information suggests that substantial risk mitigation measures would be required to meet the Annex VI triggers. No agreed reliable PECsw values are currently available to conclude on the risk to aquatic organisms.

The risk assessment for non-target arthropods was not in accordance to the ESCORT II scheme. The standard glass plate tests suggests that there will be some adverse effects on sensitive non-target arthropods. Extended lab studies gave an indication that the risk to non-target arthropods is low. Concerns were raised with regard to the comparability of the different formulations used in the studies with non-target arthropods. EFSA agrees to the assessment of the RMS that the formulations are sufficiently similar to conclude on the risk to non-target arthropods for the representative use. The applicant informed that a different formulation than Granit will be marketed. It is suggested that a risk assessment for this formulation is conducted at MSs level after the decision on Annex I inclusion.

The formulation Granit had no significant effect on organic matter decomposition over a six months period in a litter bag test at an application rate of 180 g a.s./ha and 500 g a.s./ha. The soil concentration was calculated in the DAR as 0.67 mg a.s./ha. This concentration did not cover the interim PECplateau concentration of 0.832 mg a.s./kg soil and hence a data gap was identified in the expert meeting. However it was noted after the expert meeting that the theoretical soil concentration in the litterbag-study was calculated for an application rate of 500 g a.s./ha only but should also include the rate of 180 g a.s./ha. The recalculated theoretical soil concentration of 0.907 mg/kg soil would cover the interim PECplateau concentration and hence no new litterbag-study is required.

Effects of >25% on nitrogen transformation were observed at an application rate of 400 g a.s./ha (0.53 mg a.s./kg soil). The tested concentration of 0.53 mg a.s./kg soil does not cover the interim plateau PECsoil. A potential high risk to soil micro-organisms cannot be excluded and new studies are necessary to cover the peak PECsoil concentration.

The risk to bees, earthworms, non-target plants and biological methods of sewage treatment was assessed as low.

Key words: Bromuconazole, peer review, risk assessment, pesticide, fungicide

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BACKGROUND

Commission Regulation (EC) No 1490/2002 laying down the detailed rules for the implementation of the third stages of the work program referred to in Article 8(2) of Council Directive 91/414/EEC and amending Regulation (EC) No 451/2000, as amended by Commission Regulation (EC) No 1095/2007 regulates for the European Food Safety Authority (EFSA) the procedure of evaluation of the draft assessment reports provided by the designated rapporteur Member State. Bromuconazole is one of the 79 substances of the third stage Part A covered by the amended Regulation (EC) No 1490/2002 designating Belgium as rapporteur Member State.

In accordance with the provisions of Article 10(1) of the Regulation (EC) No 1490/2002, Belgium submitted the report of its initial evaluation of the dossier on bromuconazole, hereafter referred to as the draft assessment report, received by EFSA on 14 November 2005. Following an administrative evaluation, the revised version of the draft assessment report was distributed for consultation on 5 May 2006 to the Member States and the main applicant Bayer CropScience as identified by the rapporteur Member State. The original notification had been filed by Aventis Crop Science.

The comments received on the draft assessment report were evaluated and addressed by the rapporteur Member State. Based on this evaluation, EFSA and Member States identified and agreed during a written procedure in February – March 2007 on data requirements to be addressed by the notifier as well as issues for further detailed discussion at expert level.

Taking into account the information received from the notifier addressing the request for further data, a scientific discussion of the identified data requirements and/or issues took place in experts' meetings in July and October 2007. The reports of these meetings have been made available to the Member States electronically.

A final discussion of the outcome of the consultation of experts took place during a written procedure with the Member States in February-March 2008 leading to the conclusions as laid down in this report.

During the peer review of the draft assessment report and the consultation of technical experts no critical issues were identified for consultation of the Scientific Panel on Plant Health, Plant Protection Products and their Residues (PPR).

In accordance with Article 11(4) of the Regulation (EC) No 1490/2002, this conclusion summarises the results of the peer review on the active substance and the representative formulation evaluated as finalised at the end of the examination period provided for by the same Article. A list of the relevant end points for the active substance as well as the formulation is provided in appendix 1.

The documentation developed during the peer review was compiled as a **peer review report** comprising of the documents summarising and addressing the comments received on the initial evaluation provided in the rapporteur Member State's draft assessment report:

- the comments received,
- the resulting reporting table (rev. 1-1 of 3 April 2007)

as well as the documents summarising the follow-up of the issues identified as finalised at the end of the commenting period:

- the reports of the scientific expert consultation,
- the evaluation table (rev. 2-1 of 3 March 2008)

Given the importance of the draft assessment report including its addendum (compiled version of February 2008 containing all individually submitted addenda) and the peer review report with respect to the examination of the active substance, both documents are considered respectively as background documents A and B to this conclusion.

By the time of the presentation of this conclusion to the EU-Commission, the rapporteur Member State has made available amended parts of the draft assessment report (Vol. 3 B1-B2, B5-B9) which take into account mostly editorial changes. Since these revised documents still contain confidential information, the documents cannot be made publicly available. However, the information given can basically be found in the original draft assessment report together with the peer review report which both is publicly available.

THE ACTIVE SUBSTANCE AND THE FORMULATED PRODUCT

Bromuconazole is the ISO common name for 1-[(2RS,4RS:2RS,4SR)-4-bromo-2-(2,4-dichlorophenyl)tetrahydrofurfuryl]-1H-1,2,4-triazole (IUPAC).

Bromuconazole is a conazole fungicide; other examples of members of this class are fenbuconazole and myclobutanil. It causes inhibition of C-14-demethylase in sterol biosynthesis. It is used as a broad-spectrum fungicide, with preventative and curative action, for control of diseases caused by ascomycetes, basidiomycetes, and deuteromycetes

The representative formulated product for the evaluation was "EXP10064C", a suspension concentrate formulation (SC).

The evaluated representative uses are as a fungicide on wheat full details of the gap can be found in the attached list of end points.

SPECIFIC CONCLUSIONS OF THE EVALUATION

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

The minimum purity of bromuconazole as manufactured should not be less than 960 g/kg sum of diasteromers (LS850646 + LS850647), with LS850646 (CAS 114544-80-2) ranging between 500 to 560 g/kg and LS850647 (CAS 114544-81-9) ranging between 420 to 480 g/kg. These ranges imply ratios LS850646/LS850647 between 1.04:1 and 1.33:1. At the moment no FAO specification exists.

However, since clarification is required with respect to certain impurities to confirm the proposed maximum levels in the technical material, the specification for the technical material as a whole should be regarded as provisional for the moment. The technical material contains no relevant impurities. The content of bromuconazole in the representative formulation is 200 g/L (pure).

Beside the specification, 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 bromuconazole or the respective formulation. However, the following data gaps were identified:
A dissociation constant study using OECD 112

The main data regarding the identity of bromuconazole and its physical and chemical properties are given in appendix 1.

Sufficient test methods and data relating to physical, chemical and technical properties are available. Also adequate analytical methods are available for the determination of bromuconazole in the technical material and in the representative formulation as well as for the determination of the respective impurities in the technical material.
Therefore, enough data are available to ensure that quality control measurements of the plant protection product are possible.

Adequate methods are available to monitor all compounds given in the respective residue definition, i.e. bromuconazole in food of plant origin (cereals, only) and bromuconazole in soil, water and air. It should be noted however that the residue definitions for plants and animals are provisional refer to chapter 3.

Residues in products of plant origin (cereal only) can be determined with a multi-method (the German S19 method has been validated) with an LOQ of 0.05 mg/kg. Products of animal origin are analysed by GC-ECD with confirmation by GC-MS the LOQ was 0.01 mg/kg for milk and 0.02 mg/kg for the other matrices.

Soil is analysed by GC-ECD with an LOQ of 0.02 mg/kg confirmation is by using a column of different polarity. Water is also analysed by GC-ECD with an LOQ of 0.1 µg/L with confirmation by GC-MS. Air is analysed by LC-MS/MS with an LOQ of 0.4 µg/m3. A method of analysis for body fluids and tissues is not required as bromuconazole is neither toxic nor highly toxic.

2. Mammalian toxicology

Bromuconazole was discussed in a meeting of experts in July 2007 (PRAPeR 29).

Bromuconazole is a mixture of 2 diastereomeric pairs of enantiomers (LS850646 and LS850647). The toxicological key studies have been performed with an average 52:45 ratio. Triggered by a question from PRAPeR 30 (Residues), the meeting of experts noted that in the 28 day study in rat (Broadmeadow, 1989) an increased plasmatic levels of isomer LS850646 was observed when compared to isomer LS850647, at ca. 132 mg/kg b.w./day: this might be an indication that the toxicological studies cover, only to a certain extent, a possible shift to isomer LS850646 in residues.

Based on the available information reference values for separate isomers could not be derived. A data gap was highlighted concerning the isomerisation shift in residues of isomer LS850646 against isomer LS850647, in order to show that the toxicological profile does not differ significantly from the one supported in the submitted DAR in case a different ratio is produced.

Also the issue of impurities was discussed during the meeting. All impurities were tested for acute toxicity or genotoxicity: none of the impurities showed an LD_{50} higher than the parent compound, and none showed genotoxic potential. The meeting confirmed that the batches used for the toxicological tests were equivalent to the technical specification.

It is noted that the proposed specification is provisional at the moment.

2.1. Absorption, Distribution, Excretion and Metabolism (Toxicokinetics)

Bromuconazole is rapidly absorbed in the rat. Based upon the radioactivity in bile, urine, cage wash, tissues and carcass at 48h post-dose, an absorption rate of 88% was agreed.

Bromuconazole is rapidly and almost completely eliminated; it is widely distributed in tissues, mainly in liver and kidney, fat, ovaries and uterus tissue.

Bromuconazole is extensively metabolised, through oxidation and ring-opening of the tetrahydrofurane moiety, followed by a glucuronide-conjugation or by the formation of a sulphate ester, and hydroxylation of the phenyl ring.

2.2. Acute toxicity

Bromuconazole oral LD_{50} is 328 mg/kg bw (rat study), therefore bromuconazole was proposed for classification as “harmful if swallowed” (Xn; R22). The acute toxicity by dermal and inhalation route of bromuconazole is low (LD_{50}>2000 mg/kg bw and LC_{50}>5 mg/L). Bromuconazole is neither skin nor eye irritant. It is not a skin sensitising agent.

2.3. SHORT TERM TOXICITY

The short-term toxicity of bromuconazole was assessed in rat, mouse and dog. Target organ is the liver in all species.

The dog is the most sensitive species, showing increased alkaline phosphatase and alanine aminotransferase activities together with altered albumin and globulin levels, and increased liver weight at high doses. Adverse effects in skin (erythema) and periferal lymph nodes (lymphadenitis) were observed in addition. At MTD, a slight effect on the blood occurred, with decreased RBC and Hb levels, increased MCV and platelet counts, and increased circulating WBC. It was considered that 2.5 mg/kg bw/day is the overall relevant NOAEL in dog.

During the meeting of experts the NOAEL in the 90 day rat study was discussed. The RMS set the NOAEL at 40 ppm (=2.7 mg/kg bw/day) based on fatty vacuolation at the next higher dose of 200 ppm. This value was considered to be in line with the relevant NOAEL in dogs.

However, the fatty vacuolation at 200 ppm represented a very borderline case, since it occurred in only 2 females out of 10, without any other effects. The meeting finally agreed to set the NOAEL in rat at 200 ppm (=13.8 mg/kg bw/day) taking into account the (mild) nature of the findings at 200 ppm.

2.4. GENOTOXICITY

Bromuconazole was tested in 6 *in vitro* and 2 *in vivo* tests. There was some indication of weak clastogenicity *in vitro*, in the presence of exogeneous rat metabolisation. The compound could also be considered weakly positive at cytotoxic doses, in one out of two mammalian gene-mutation assays, but was negative in the bacterial genotoxicity battery. There was no indication that the compound elicited UDS in rat liver cells *in vitro*. No positive results were generated *in vivo*, neither in the micronucleus assay nor in the UDS assay.

Overall, bromuconazole was considered devoid of genotoxic potential.

2.5. LONG TERM TOXICITY

As in subchronic toxicity studies, also for long term exposures liver was the target organ (hepatocyte fatty vacuolation, liver enlargement at necropsy, nodular hyperplasia) in both rats and mice.

The relevant NOAEL of 20 ppm (0.88 mg/kg bw/day) was selected from the rat study, mainly based upon the increased hepatocyte vacuolation in females.

Carcinogenic potential of bromuconazole was discussed in the meeting of experts. Treatment-related neoplastic lesions (exceeding historical control data) in rats occurred at the top-dose in females, where two animals showed hepatocellular carcinoma and one a cholangiocellular carcinoma. Mice showed hepatocellular carcinoma at high doses (the incidence was just outside the historical control range). In both rats and mice, the tumours occurred at the top-doses, likely caused by liver toxicity and subsequent cell renewal. The tumours could also be considered as incidental, since the mechanism of action was not clearly elucidated. In both cases, they would not trigger classification.

The meeting agreed to keep the NOAELs as set by the RMS (20 ppm in rat and mouse) that would cover the occurrence of tumours at high doses.

It was agreed that bromuconazole does not have carcinogenic potential relevant to humans.

2.6. REPRODUCTIVE TOXICITY

In a two-generation study, bromuconazole caused maternal toxicity at 200 ppm (13.8 mg/kg bw/day) and above (decreased body weights). In addition, a slight increase of pre-coital interval and gestation length occurred in the F0-generation, and adult F0/F1 animals also showed increased liver weights, associated with hepatocyte fatty vacuolation at the top-dose. F2 generation showed slightly decreased body weight gain at 200 ppm. Both parental and foetal toxicity NOAEL were established at 20 ppm, corresponding to 1.3 mg/kg bw/day. It was concluded that bromuconazole is not reprotoxic to the rat, and the reproductive NOAEL was established at the highest dose of 141 mg/kg bw/day.

As for developmental toxicity, in the rat the relevant maternal NOAEL is 70 mg/kg bw/day; at the same dose onwards a dose-dependent increase of placental weight was considered a sign of foetal toxicity together with ossification delays or supernumerary bones in a number of skeletal structures. Therefore, it was concluded that 10 mg/kg bw/day is the developmental NOAEL. The higher prevalence of supernumerary cervical ribs was considered possibly relevant for humans. Increased placental weight was not observed in the rabbit, but in the absence of a valid mechanism of action, it was considered potentially adverse.

In the meeting of experts, the classification as reproductive toxicant Class 3 (Xn; R63, 'May cause harm to unborn child') proposed by the RMS was discussed. It was noted that usually supernumerary ribs are considered as variations rather than as malformations. But, indeed they appeared at doses were no maternal toxicity was observed. It was considered that the "domed head" (a hydrocephalus like malformation) was a typical observation upon exposure to triazoles. The findings were confirmed in a study with dermal application and supported by the occurrence of typical triazole induced malformations at high doses. The meeting agreed to propose classification as R63.

2.7. NEUROTOXICITY

Bromuconazole does not have structural relationship with organophosphate compounds or compounds known for neurotoxicity/delayed neurotoxicity potential. No studies are available and they are not required.

2.8. FURTHER STUDIES

The metabolite LS860364[2] was considered an intermediate in the rat metabolism study (debromylated intermediate before 5-hydroxylation of the tetrahydrofurannic cycle of bromuconazole). It was recovered as a fish, plant and soil metabolite. In the rat, LS860364 was not more toxic than bromuconazole (LD_{50} 1347 mg/kg bw); it is negative for genotoxicity *in vitro*.

The impurities LS880225, LS880226, RPA 405516, RPA 405517 were of the same toxicity as bromuconazole whereas RPA 400063 and RPA 400064 showed lower toxicity. Therefore, no further assessment of their toxicological profile was triggered.

[2] LS860364: 1-[2-(2,4-dichlorophenyl)-2,5-dihydrofuran-2-ylmethyl]-1H-1,2,4-triazole

2.9. MEDICAL DATA

Annual health surveillance data submitted by the applicant, including examination of lung function, haematology and biochemistry and skin condition, did not reveal abnormal results. No epidemiological studies involving exposure to bromuconazole are available. No data from the open medical literature are published.

2.10. ACCEPTABLE DAILY INTAKE (ADI), ACCEPTABLE OPERATOR EXPOSURE LEVEL (AOEL) AND ACUTE REFERENCE DOSE (ARFD)

Acceptable daily intake (ADI)

The ADI of 0.01 mg/kg bw/day was set based on the relevant long term toxicity/carcinogenicity NOAEL of 0.88-1.09 mg/kg bw/day from the 2 year rat study, applying an SF of 100.
For the developmental effects in rats there is margin of safety of 7000.

Acute reference dose (ARfD)

For the ARfD, the meeting agreed to base the value on the developmental NOAEL of 10 mg/kg bw/day from the rat study, with an SF of 100, leading to an ARfD of 0.1 mg/kg bw.

This ensures a MOS of more than 2000 in respect to the major findings of the study (malformations at the top dose) and 700 for the supernumerary cervical ribs occurring at 70 mg/kg bw/day.

Acceptable operator exposure level (AOEL)

The dog appeared to be the most sensitive species. The AOEL was set on basis of the NOAEL of 2.5 mg/kg bw/day from the 90-day dog study (applying a standard SF of 100).
The AOEL was set at 0.025 mg/kg bw/day.

EFSA note: during the commenting phase of the draft conclusion, SE commented that the NOAEL from the 2 generation study is lower than the 90-day dog study NOAEL and relevant for the setting of an AOEL of 0.014 mg/kg bw/day (SF 100) based on decrease body weight changes on pups and maternal. The data package included in the DAR would show that the pups and pregnant rats are more sensitive to the treatment of bromuconazole than adult animals. SE also noted that the outcome from the Operator exposure would not change using the proposed AOEL. However, it could be important at national level for the registration of other products containing bromuconazole.

2.11. DERMAL ABSORPTION

During the meeting of experts, the submitted *in vitro* studies (Walters 1990, 1991) were analysed, showing several shortcomings (mass balance absent, application site radioactivity disregarded), making the studies hardly acceptable.

The meeting agreed to dismiss the *in vitro* studies and to use the values from the *in vivo* study. It was decided to consider for the representative formulation Granit EXP 10064 dermal absorption values of 5% and 45% for the concentrate and the dilution, respectively.

2.12. EXPOSURE TO OPERATORS, WORKERS AND BYSTANDERS

The formulation of bromuconazole, a suspension concentrate (SC) containing 200 g/L Bromuconazole is proposed to be used as a fungicide in foliar application on cereals.

Operator exposure

	Application method (crop)	Treated area (ha/day)	Systemic exposure (mg/kg bw/day)	% of systemic AOEL
German model	Tractor, field crops	20	0,05941 mg /kg bw/day 0.003858 mg /kg bw/day	240 15.6*
UK POEM	Tractor, hydraulic boom and nozzles	50	0.3293 mg/kg bw/day 0.05021 mg/kg bw/day	13172 200°

*Gloves during M/L and application and coveralls and boots during application
°Gloves during M/L and application

The operator exposure is estimated to be below the AOEL only for the calculations with German model and considering the use of PPE (gloves during M/L and application and coveralls and boots during application).
EFSA notes that the correct calculations are presented in the revised DAR (June 2007), but not in the toxicology Addendum to the DAR submitted in June 2007.

Worker exposure

The worker exposure was estimated according to the following equation:
$D = DFR \times TF \times AR \times P$,
where:
- DFR is the dislodgeable foliar residue
- TF is the transfer factor
- WR is the working rate
- AR is the application rate, which is maximally 0.2 kg a.s./ha
- P is the penetration factor

Assuming a DFR=0.003 mg a.s./cm², a transfer factor TF=5000 cm²/person/h (field-crop estimation), a working rate of 1h/d (scouting task), and a default penetration factor (PPE used)=5%, and a skin absorption of 45%,

D = 0.003 mg /cm² × 5000 cm²/person/h × 1/60 kg× 1h/day × 0.2 kg/ha × 0.05 × 0.45 = 0.00114 mg /kg bw/day

The estimated exposure for re-entry activities (scouting) is 4.5% of the AOEL.

EFSA notes that the correct calculations are presented in the revised DAR (June 2007), but not in the toxicology Addendum to the DAR submitted in June 2007.

Bystander exposure

During the meeting of experts, RMS was asked to re-calculate bystander exposure considering that bystander's clothing does not provide a 100% protection to the spray drift.

RMS recalculated the dermal exposure, taking into account the greatest possible exposed skin area, 2 m² instead of 0.4225 m². In this case, the dermal exposure would be 0.00039 mg/kg b.w.; together with the inhalation exposure, equivalent to 0.044% of the AOEL, the total exposure would be 1.6% of the AOEL.

3. Residues

Bromuconazole was discussed in the meeting of experts in residues PRAPeR 30, round 6 in Parma in July 2007.

Bromuconazole is a mixture of two diastereomeric pairs of enantiomers (4 bromuconazole isomers). The ratio of the diastereomers LS850646 and LS850647 is not defined, but the substance used in the submitted tests and studies had a ratio of diasteromers ranging between 1.04 : 1 and 1.33 : 1. The ratio of the enantiomers in each diastereomer was not reported but is assumed to be approximately 1 : 1.

All metabolism studies (plants and livestock) were performed using phenyl-labelled bromuconazole only, and thus the fate of the triazole moiety of the molecule was not investigated.

Initially, the RMS considered that studies with a radiolabel on other moieties than the phenyl-ring are not required because cleavage of the compound does not seem to occur. However, in studies with wheat a considerable part of the total radioactive residues (TRR) was not identified. It is not known whether these residues still contain the triazole moiety. Therefore, in PRAPeR 30 meeting the RMS and the experts agreed that cleavage of the molecule cannot be excluded and further investigation of the triazole moiety is required. Triazole derivative metabolites are expected to be of toxicological concern and to prove their presence or absence is considered essential for a reliable risk assessment.

Therefore the meeting of experts proposed a general data gap for the exposure of the consumer to triazole derivative metabolites to be addressed for all areas i.e. primary crops, rotational crops, and animal matrices.

3.1. NATURE AND MAGNITUDE OF RESIDUES IN PLANT

3.1.1. PRIMARY CROPS

Plant metabolism was investigated in wheat, representative for cereal crops and in apples and bananas, representative for the category of fruit crops.

In a study on wheat, following foliar applications according to the representative GAP (*ca* 1N rate) and soil treatment (corresponding to *ca* 0.75 N rate of a foliar treatment), respectively, the amount of volatile residues was very low. After soil treatment less than 1% and after foliar treatment less than 0.1% of the applied radioactivity was recovered as volatile residues.

After foliar application most of the radioactivity was located in the leaves and stems (24.3 mg/kg) while residues in grain were low (0.04 mg/kg). Large portions of the residue were unavailable for solvent extraction, in particular in the grains (44% TRR). Bromuconazole represented a significant portion of the extractable residues in all plant parts. In the leaves and stems extracts, about 51-64% of the radioactivity was identified as bromuconazole (corresponding to *ca* 38-48% TRR in leaves and stems) and in grain 49% of the extractable radioactivity co-eluted with the bromuconazole isomers (corresponding to *ca* 27% TRR in grain). Upon acid hydrolysis a decrease in polar compounds and an increase of less polar metabolites including bromuconazole was observed, indicating the presence of conjugates of bromuconazole and its metabolites.

After soil treatment, a constant uptake and translocation of radioactivity to aerial plant parts was observed, so that at harvest a considerable part of the radioactivity was located in the leaves and stems (5.7 mg/kg). Total residues in grain were low (0.15 mg/kg) but found to be an order of magnitude higher than following a foliar treatment. Bromuconazole represented ca 6 - 15% of the radioactivity in leaves and stems extracts (corresponding to *ca* 4-10 % TRR) while most of the extracted radioactivity remained unresolved (68-93%). Residues in grains were not further investigated.

In a second study, wheat plants were treated by foliar application according to the representative GAP (1N rate). At harvest, the main constituent of the total residue in all investigated wheat matrices i.e. grain, chaff and straw was bromuconazole (mixture of diastereomers, free and conjugated), corresponding to 16-35% TRR. In wheat grains, metabolite C was also found at significant levels (12% TRR). It was not identified, but could be characterised as a multi-component fraction. A significant amount of the residue in the tested wheat matrices remained unknown (21-45% TRR). In straw and chaff, this unknown fraction consisted of several metabolites present at low levels, none of which represented more than 2.5 % of the TRR. In grains however, the unknown fraction consisted mainly of multiple small fractions which were not further analysed. The largest un-analysed individual fraction represented approximately 20 % TRR. However, this unknown radioactivity was found to be polar in nature, even more than the unidentified metabolites in straw and chaff. This might indicate an extensive metabolism. The study analysed residues of bromuconazole for its diastereomers LS850646 and LS850647, but not for the enantiomers in each diastereomer. Results of the composition of the final bromuconazole residue indicated a shift towards the LS850646 isomer (ratio about 70: 30 in straw and grain and 92: 8 in wheat chaff).

Although no uses in fruit have been supported in the EU peer review, metabolism studies with bromuconazole in apples and bananas following brushing and spraying of individual fruits, respectively, were submitted and evaluated.

In the study on bananas migration of the residue to the pulp was very low and residues were mainly found on the peel. Bromuconazole was not extensively metabolised by the banana plant within 30 days after treatment, and hence represented the major part of the residue (78% TRR in peel, 98% in pulp). The data suggest there was only little change in the diastereomer ratio (from initially 1.22 : 1 to 1.78 : 1 in banana pulp; however based on very low residue levels and therefore not conclusive). Minor metabolites (0.5- 2%TRR) could be identified as debrominated metabolite (LS 860364), 3-hydroxy metabolite (LS 860550/860551), 2-ketone metabolite (LS 870353) and 5-H-2-ketone metabolite (RPA 401527). The level of conjugated metabolites in banana peel and pulp was low (1% TRR).

The study in apples demonstrates a small translocation of the residues into the pulp of the fruits after application to the apple surface, but the residues remain principally in the peel. Most of the radioactivity present at harvest (78 days after application) was extractable with methanol (79-95%TRR), however identification rate of extracted radioactivity from peel and pulp was low (7-15% TRR). Mainly identified was bromuconazole (12% TRR in peel, 3% TRR in pulp). The ratio of isomers of bromuconazole was not investigated. Formation of hydroxylated metabolites (LS 850920 and RPA 406117) (together <5% TRR) and conjugates was found to a minor extent. The majority of radioactivity was characterised as fractions consisting of several metabolites (individually < 10% TRR) that were not further analysed. A shortcoming of the apple study with regard to storage stability data was identified, however this is not relevant for the assessment of the notified use in cereals, but may for future uses need to be assessed at member state level.

Based on the studies on wheat, banana and apple, the metabolic pathway shows the elimination of bromine followed by hydroxylation and oxidation of the furan ring with an eventual conjugation of the metabolites. A major part of the residue remains as bromuconazole, however, given the predominance of the diastereomer LS850646 in the terminal residue a stereoselective metabolism is assumed in cereals. The available data don't permit a conclusive statement on whether or not stereoselective metabolism may also occur in fruits. It is noted that none of the plant metabolism studies investigated the ratio of enantiomers in each diastereomer.

The meeting of experts agreed from the available plant metabolism data it was not possible to conclude on the residue definition because there were no triazole-ring labelled studies. The meeting concluded that a triazole-ring labelled study is required for cereals. The provisional residue definition for risk assessment and monitoring purposes was agreed as bromuconazole (sum of isomers). The proposed definition is currently limited to the supported use in cereals.

Supervised residue trials were carried out according to the supported representative use on wheat in Northern and Southern Europe. The two diastereomers of bromuconazole were analysed separately in all samples. No data was submitted on the ratio of enantiomers in each diastereomer of

bromuconazole. Residues in grains were consistently below the LOQ (0.005 mg/kg or 0.01 mg/kg respectively) for either diastereomer. In straw residues of LS850646 and LS850647 were with few exceptions consistently above the LOQ (0.025 mg/kg for each diastereomer). The straw results confirmed the observation in the radiolabel studies of a shifted isomer ratio of LS850646 and LS850647 (in average 70: 30, exceptionally around 80: 20)

Based on the trial results HRs (Highest Residues) and STMRs (Supervised Trials Median Residues) could be derived for each relevant data set on grains and straw and an MRL could be proposed for wheat grain. (refer to 3.4) Valid storage stability data for the individual diastereomers of bromuconazole support the residue values found in supervised residue trials.

No investigation of the behaviour and the level of residues under processing conditions has been necessary due to the insignificant level of residues in wheat grain. Straw is usually not processed.

3.1.2. SUCCEEDING AND ROTATIONAL CROPS

The DT_{90} for bromuconazole ranges between 170 and 709 days. Investigation of residues in rotational crops was therefore necessary.

A confined rotational crop study with ^{14}C-bromuconazole (phenyl labelled) was conducted using radish, lettuce, mustard and wheat planted after aging of the treated soil (1.5N rate) for 1 month, 3 months and 1 year. The results indicate an up-take of residues by crops from soil. Significant residue levels were found in wheat, especially in the straw (up to 0.62 mg/kg) and in the forage (up to 0.13 mg/kg). The levels of radioactivity found in radish, wheat grain, lettuce and mustard ranged between 0.01 and 0.04 mg/kg, depending on the pre-plant interval. Samples of lettuce, mustard and wheat grain were not further analysed.

Upon analysis of the extracted radioactivity from wheat and radish samples bromuconazole was the main constituent (13 - 56%) of the total residue. Bromuconazole levels up to 0.08 mg/kg were found in straw, 0.05 mg/kg in forage and 0.02 mg/kg in radish roots. As observed in primary metabolism crop studies, residues of the bromuconazole diastereomer LS850646 were higher than that of LS850647, suggesting stereo specific processes also in rotational crops, however no data is available on the ratio of isomers in soil to draw any firm conclusion. The ratio of enantiomers in each bromuconazole diastereomer was not investigated.

Metabolites were identified that had also been found in the primary crop studies, but none of them was present at levels above 0.01 mg/kg. In addition a number of unidentified metabolites could be characterised and showed an intact phenyl-triazole bond. The metabolic pattern in rotational crops and directly treated crop was found to be similar.

However, as only phenyl labelled bromuconazole was used and a large portion of radioactivity was not identified, no information is available on whether or not triazole derivative metabolites might have been present in the crops. Therefore, the meeting of experts identified a data gap for a rotational crop metabolism study with triazole-labelled compound.

In rotational crop residue trials the level of bromuconazole residues was investigated in cereals. Wheat was sown between 30 and 300 days after an application of bromuconazole to the preceding wheat plants. However, it is noted that the application rate in the trials was only half the critical rate

(0.5 N) of the notified representative use. At harvest of the rotational wheat, bromuconazole levels in grain and straw were all below the LOQ of 0.02 mg/kg for grain and 0.05 mg/kg for straw, respectively. In wheat forage residues up to 0.02 mg/kg were found at the shortest pre-plant interval of 30 days.
A further study on the level of residues in rotational leafy crops and turnips was considered not acceptable by the RMS as important data is missing in the report.

Taken the information from the confined study and the rotational wheat residue trials together, the experts concluded that residues of bromuconazole *per se* are not expected to occur in rotational crops above the LOQ of the monitoring method (multi method; 0.05 mg/kg) when bromuconazole is used according to the notified cGAP in cereals. With regard to whether triazole metabolites may reach quantifiable levels in rotational crops no conclusion is currently possible. Therefore, the meeting of experts proposed a data gap for a rotational crop metabolism study with a triazole label.

The meeting concluded that for other uses than the assessed GAP in cereals the residue situation in rotated crops needs to be reconsidered.

3.2. NATURE AND MAGNITUDE OF RESIDUES IN LIVESTOCK

Related to the representative use in wheat, significant levels of bromuconazole are mainly expected in straw. The theoretical intake of bromuconazole exceeds the trigger value of 0.1 mg/kg total diet for cattle. Moreover, based on its log $_{Pow}$ bromuconazole is classified as fat soluble what indicates a risk for accumulation of residues in animal tissues. Hence, metabolism and excretion of residues were studied in lactating cows and goats following repeated oral administration of ^{14}C phenyl- labelled bromuconazole.

In the study with cows (0.04 and 0.4 mg/kg bw/d), identification and characterisation of metabolites was limited to urine and faeces. However, it could be concluded that the major route of elimination of radioactivity after oral absorption is via the urine (66-82% of administered dose), most probably by conjugation of bromuconazole (*ca* 5-14% TRR) and its metabolites. The residue in the faeces (15% of administered dose) is composed of bromuconazole (*ca* 10-40% TRR) and of conjugated compounds. None of the metabolites in urine and faeces were properly quantified, but a metabolic pathway was postulated based on the qualitative findings by retention time comparison. This metabolic pathway proposes the elimination of bromine followed by hydroxylations, oxidations and finally conjugation.
Elimination through the milk was very low and a plateau was reached after two days. At sacrifice, significant levels of radioactivity were found in low-dose-group liver (0.08 mg/kg), kidney (0.04 mg/kg) and subcutaneous fat (0.03 mg/kg). Residues in fat were not further investigated. In liver and kidneys, attempts for identification were not successful, but it was demonstrated that the extracted residue is composed of a whole range of minor components. Only minor levels of bromuconazole were identified in the liver.
In a second study with lactating goats (1 and 20 mg/kg feed DM) the majority of the administered radioactivity was recovered in urine (66-70%) and faeces (21%). Elimination through the milk was

very low (<0.1%) and a plateau was reached after 24 hours. 0.3-0.4% of the administered radioactivity were recovered in tissues and organs. Upon characterisation of residues in excreta, tissue and organs, bromuconazole was recovered in faeces (*ca* 10% TRR), liver (2-3% TRR) and kidney (1% TRR) while no bromuconazole was found in urine and milk samples. Of the two diastereomers, LS850646 appeared to be the predominant one in the liver while in faeces the diastereomer ratio of the unabsorbed bromuconazole was about 1:1, suggesting a preferential metabolism of one diastereomer in the goat upon absorption of the compound. The ratio of enantiomers in each bromuconazole diastereomer was not investigated.

Identification of metabolites in the goat study was not successful and the metabolic pathway postulated based on the study with cows could not be confirmed. The distribution of radioactivity, however, is similar to the one observed in the cow study and, considering the exposure levels in practice, significant residues are only expected in liver and kidney. In these two tissues, bromuconazole was found at very minor levels. The remaining residue was not identified, but the major part of this residue was released after enzymatic hydrolysis and significant parts of it were water soluble. This might indicate the presence of polar multi-component fractions, which is consistent with the large range of metabolites observed in rat metabolism studies.

Taken all provided information together it can be concluded that administered bromuconazole is largely excreted via the urine upon a rapid metabolisation in the animal body. Significant residues were only found in metabolising organs. Identification of individual metabolites in organs and tissues was not successful. A metabolic pathway in ruminants was postulated based on identification of metabolites extracted from urine and on tentatively identified metabolites from faeces.

Although intakes of bromuconazole by poultry are not expected to be significant, hen metabolism data with radiolabelled bromuconazole was submitted and evaluated in the DAR. The administered radioactivity was mainly recovered in the excreta (89-92%). Residues in eggs and tissues were low (together 0.5% of the administered dose) In egg whites, steady state conditions were not clearly observed as levels of radioactivity were very variable within time, while in egg yolks, radioactivity levels were more consistent and reached steady state conditions after 4-5 days upon first dosing.

Upon characterisation of residues bromuconazole (both isomers) was identified as a major component in the egg yolk (14-22% TRR) and egg white (30-38% TRR), in the abdominal fat (39% TRR) and in skin with attached fat (37% TRR). There were only occasional finding of low levels (ca 1% TRR or less) of bromuconazole in hen excreta samples, livers and muscle samples. A significant shift of the ratio of bromuconazole diastereomers was found in egg white residues, that seemed to increase with duration of dosing (from 16 : 1 at day 5 up to 29 : 1 at day 14 of dosing), and some isomer shift was also observed in egg yolk (1.6 : 1 to 2.1 : 1). The ratio of enantiomers in each bromuconazole diastereomer was not investigated.

Identification of metabolites was mainly carried out from hen excreta samples, and based on the qualitative findings a metabolic pathway was postulated. This pathway shows elimination of bromine followed by hydroxylation and oxidation. Eventually, metabolites are all conjugated resulting into sulphate esters and glucuronides.

The livestock studies indicated that bromuconazole is extensively absorbed, metabolised and rapidly eliminated via the excreta. Elimination through milk or eggs is a minor route and significant residues are not expected in these tissues when assuming a realistic intake. After sacrifice, significant levels of radioactive residues were only encountered in liver and kidney.
Identification of metabolites in tissue and organs was very poor, and metabolites were only identified in the excreta. The nature of the residue in edible tissues remains unknown, especially in liver and kidneys. Nevertheless, most of the unidentified metabolites were characterised as polar and were only released after enzymatic digestion. This indicates an extensive degradation and is consistent with rat metabolism studies.
Livestock metabolism studies were only performed using phenyl-labelled bromuconazole and the fate of the triazole moiety was therefore not properly investigated in these studies. As concluded for crops, the exposure of the consumer to triazole metabolites needs to be addressed for all areas including animal matrices. It should be noted that it is likely that this will require a ruminant metabolism study with a radiolabel in the triazole moiety as there were considerable amounts of unidentified radioactivity in the studies already provided.
Therefore, it was proposed by the experts to preliminarily define the residue in edible animal matrices as bromuconazole (sum of isomers) for monitoring and risk assessment purposes. Whether in relation to the use of bromuconazole the triazole metabolites will have to be defined as a relevant residue in food of animal origin remains open at this stage.

On the basis of the available ruminant metabolism data and the estimated livestock dietary burden from the notified cereal uses no total residues above the LOQ are expected to occur in food of animal origin. Therefore at this stage livestock feeding studies are not required and MRLs for the residue definition bromuconazole can be proposed at LOQ level of the analytical method for monitoring purposes.

The meeting of experts highlighted that for the future further consideration of the livestock data may be required when other uses are intended.

3.3. CONSUMER RISK ASSESSMENT

There are no acute or chronic intake concerns for all categories of consumers considering the residues of bromuconazole *per se* from the representative use, as bromuconazole is virtually not present (not quantifiable) in food of plant and animal origin when applied according to the notified cGAP in wheat. Theoretical maximum daily intake (TMDI) estimates, based on the limit of quantification and WHO European and national consumption data (UK, Germany) range between 3 and 15% of the ADI. The estimate short term intakes (IESTI) are below 1% of the ARfD.
However, the metabolism of bromuconazole may lead to residues of triazole derivative metabolites that are considered of concern due to their toxicological profile. In the absence of residue data investigating the fate of the triazole moiety of the bromuconzole molecule the consumer exposure to those compounds cannot be assessed and thus the consumer risk assessment cannot be concluded on with regard to the triazole derivative metabolites.

It should also be noted that currently insufficient toxicological data is available to address other ratios of isomers than those tested with the bromuconazole batches used in the toxicological studies (refer to chapter 2 of this document). A shift of the diastereomerratio LS850646 / LS850647 beyond that margin was observed in plant and livestock metabolism studies.
However in terms of the cereal use notified and to be assessed in the Peer Review the consumer exposure to either bromuconazole diastereomeric pair of enantiomers is expected to be insignificant and thus no particular consumer risk with regard to the ratio of isomers has been identified.
For other uses than the representative use the issue should be carefully reconsidered.

3.4. PROPOSED MRLS

MRLs were proposed for bromuconazole (sum of isomers) on the basis of the available residue data for wheat and the findings in the ruminant metabolism studies.

Wheat grain	0.05* mg/kg
Milk	0.01* mg/kg
Ruminant meat	0.02* mg/kg
Ruminant fat	0.02* mg/kg
Ruminant liver	0.02* mg/kg
Ruminant kidney	0.02* mg/kg

It is noted that, as for other triazole pesticides, the monitoring residue definition is provisional, since at the moment no conclusion is possible whether triazole derivative metabolites might need to be included in the residue to be monitored

4. Environmental fate and behaviour

Bromuconazole was discussed at the PRAPeR experts' meeting for fate and behaviour in the environment (PRAPeR 27) in July 2007, on the basis of the DAR and the revised DAR dated June 2007. It should be noted that the methods of analysis used in all the fate and behaviour studies were not stereoselective. Therefore the regulatory dossier provides no information on the behaviour of each individual bromuconazole isomer in the environment, except for the adsorption/desorption properties. As a result, all residues reported as bromuconazole in this conclusion are for the sum of the two diastereomeric pairs of enantiomers. It is not known if either isomer is degraded more quickly than the other in the environmental matrices studied.

4.1. FATE AND BEHAVIOUR IN SOIL

4.1.1. ROUTE OF DEGRADATION IN SOIL

In a laboratory (dark, aerobic, 22 ºC, 80% moisture capacity at 0.33 bar) study on 2 loamy sand soils dosed with [phenyl-^{14}C]-bromuconazole, mineralization to CO_2 was low, accounting to 1.3-4.4% AR

after 120 days. At this incubation time, the non-extractable radioactivity reached 10.2-17.6% of the applied radioactivity. Several minor metabolites were detected, none accounted for more than 1.5% AR at any sampling time. In a supplemental study performed with an exaggerated dose, some of these degradation products were identified.

Under dark anaerobic conditions in the laboratory, the major metabolite **M4**[3] was formed at maximum level of 10.1% AR at day 181 and no other resolved unidentified components in extracts accounted for > 1.5% AR. No mineralisation occurred in the study. At the meeting of experts it was agreed that no further assessment with respect to anaerobic conditions is required for bromuconazole.

In laboratory soil photolysis study the degradation rate of bromuconazole was faster in the irradiated samples (non linear single first order DT_{50} = 78 days, summer sunlight at 50ºN latitude) than in dark controls (DT_{50} = 296 days). Therefore, photolysis may contribute to the degradation of bromuconazole at the soil surface. No novel extractable breakdown products were identified in addition to those found in dark experiment and never exceeded 2.6% AR at any sampling point.

4.1.2. PERSISTENCE OF THE ACTIVE SUBSTANCE AND THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

Additionally to the study presented under the route section, rate of degradation of bromuconazole in soil was also investigated in another soil at 20ºC at 60% field capacity and different incubation conditions (sterile, reduced dose and reduced moisture). According to Annex II data requirements, further laboratory aerobic rate of degradation study should be provided on an additional soil. However, there was agreement by the experts that the available data with 3 soils already indicate that field studies are triggered and it was concluded that no further degradation rate studies in soil are needed. Degradation rates were re-calculated using single first order non linear regression and indicated that bromuconazole can be classified as high to very high persistent (DT_{50} = 329-1028 day at 20-22ºC).

Field dissipation of bromuconazole was investigated in 7 locations in Germany. In the original reports[4] the essential information on the field phase (sites description and history at the trial sites, characterisation of the soils profile, applied formulations and doses, sampling details, climatic data) were not reported. Concerns were raised also on the kinetics and the correlation coefficient for the estimated DT_{50} values. In the updated DAR (June 2007), the RMS indicated that the GLP trials were conducted at sites where the soil and weather conditions are typical of those found at locations where bromuconazole could be used, but no additional information to support the argumentation was provided by the RMS. Re-calculated field dissipation DT_{50}s using non-linear regression together with the goodness of fit were also provided in the revised DAR. The experts on fate and behaviour agreed that the field dissipation studies should not be considered valid because too much crucial information on the experimental design were not available and therefore a data gap was identified for adequate

[3] M4 = 2-(2,4-dichlorophenyl-2-(1,2,4-triazol-1-yl methyl)) tetrahydrofuran (LS 871387).

[4] (I) Fischer (1993). Bromuconazole. Determination of its residue in soil samples of the Rhône-Poulenc Agro study no.90-197. A&M, Cologne, Germany. Report n° A & M 025/92, BCS n° C016643. (II) Lenz (1994). Analytical determination of residues of the active ingredient bromuconazole from the outdoor study RPA10064F. Biochem GmbH, Karlsruhe, Germany. Report n° Biochem 91 50 10 140. BCS n° C016419

field dissipation studies. During the meeting it was also highlighted the need for a good estimate of microbial degradation from these field studies for modelling purposes, that is to say that the kinetic assessment of the study design of any new studies would need to exclude the photolytic degradation that is expected to occur at the soil surface. Further information on the field trials (soil classification, soil pH and organic carbon content, application rate and type of growing crop) were provided in a revised version of the DAR dated January 2008, which is not peer reviewed. Although the additional data partially address the perceived inadequacies of these field studies, the EFSA is of the opinion that the results should not be used as input to FOCUS modelling or any other assessment that needs a microbial degradation rate as input. As only 3 reliable laboratory DT_{50} values are available, the longest laboratory DT_{50} value is therefore considered adequate for PECs calculations. In the discussion at PRAPeR 27, the value of $DT_{50\ 22^{o}C}$ = 1028 d was indicated to be used in modelling, taking into consideration that this would be a first tier assessment that may result in an overestimation of PECs. On the contrary, according to the RMS, the field DT_{50} that have been proposed in the DAR should be considered valid and suitable to calculate the environmental exposure concentrations used for risk assessment.

The potential for soil accumulation of bromuconazole was investigated in one study with annual application to continuous spring cereals (1 trial in Germany and 1 trial in UK). The studies indicated that accumulation may occur (2.56 times the single application rate); however, the plateau concentration was not reached in the German site after four years. Re-calculation of normalized field dissipation rate for bromuconazole from soil accumulation data was provided in the updated DAR (June 2007). The experts agreed with the RMS assessment that accumulation studies are adequately documented but do not contain enough data points to derive reliable dissipation and/or degradation rates for bromuconazole.

The meeting of experts concluded that the best data available with respect to the potential accumulation in soil was the maximum level of 0.624 kg a.s./ha reached in the field accumulation study, equivalent to 0.832 mg a.s./kg soil (assuming a soil mixing depth of 5 cm and soil bulk density of 1.5 kg/L). It was agreed that this value can be used for a provisional risk assessment to soil organisms. As a consequence of the lack of data on reliable biodegradation rate under field conditions, a data gap was identified in PRAPeR 27 for new PECsoil calculations.

4.1.3. MOBILITY IN SOIL OF THE ACTIVE SUBSTANCE AND THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

The soil adsorption/desorption characteristics of the two diastereoisomers (LS850646 and LS850647) contained in bromuconazole were determined separately in one batch adsorption/desorption study is available for bromuconazole with 4 soils (pH 5.7-8.0; organic carbon content: 0.46-2.44%). The results showed that the adsorption pattern fits the Freundlich equation, with $K_f oc$ values ranging from 474 to 1086 mL/g for isomer LS850646 (1/n = 0.78-0.85) and from 627 to 1539 mL/g for isomer LS850646 (1/n = 0.76-0.86). There was no indication of adsorption being pH dependant. It was agreed in PRAPeR 27 that the mean $K_f oc$ value of 757 mL/g and 1/n = 0.82 were the appropriate values for bromuconazole as input parameters for FOCUS modelling.

Laboratory soil column leaching studies were performed with either freshly-applied or after aerobic incubation for 30 days in four soils. The results showed a low mobility for bromuconazole with maximum 0.6% AR and 2% AR recovered in the leachate of the fresh residue and aged residue experiment respectively. The nature of the radioactivity (62.4-97.6% AR) indicated that bromuconazole and very minor metabolites (no further identified) were retained in the top 6 cm soil layer.

In another study the leaching of bromuconazole was investigated in two soils, following an aging period of 210 days. Analysis of the leachates and soil segments showed that movement was limited and that metabolites (each less than 2.5% AR) and unextracted residues remained primarily in the top 5 or 10 cm of the soil leaching columns.

4.2. FATE AND BEHAVIOUR IN WATER

4.2.1. SURFACE WATER AND SEDIMENT

Bromuconazole was essentially stable under sterile hydrolysis conditions at 25ºC at pH 4, 5, 7 and 9.

A study with the UV-adsorption properties of bromuconazole in water at pH 4 and pH 9 was submitted. Results indicated that bromuconazole will not undergo direct aqueous photolysis at pH and that photolysis in aqueous solution is pH dependent (with an estimated DT_{50} of 18 days at pH 4). However, some deficiencies in the recovery of the applied radioactivity in the study conducted at pH 4 were observed. In addition, during the peer review, concerns were raised by the experts of the physical/chemical properties section on the pH 4 buffer constituents: it was not clear if they were contaminated or contained some impurity that acted as a photosensitizer. The issue could not be transferred to the fate section as bromuconazole was discussed in the section on physical-chemical properties after the PRAPeR 27 meeting. However, as the molar adsorption coefficient (ε) at a wavelength ≥ 290 nm is < 10L mol^{-1} cm^{-1} it can be concluded that photolysis is not expected to be a significant process in the breakdown of bromuconazole in natural aquatic systems.

A ready biodegradability test (OECD 301B) indicated that bromuconazole is “not readily biodegradable” using the criteria defined by the test.

The water-sediment study (2 systems studies at 20ºC in the laboratory) demonstrated bromuconazole dissipated quite rapidly from water by partitioning to sediment (first order multicompartment $DT_{50\ water}$ of 1.3-2 days; $DT_{90\ water}$ of 53.8-235 days) where it subsequently degraded slowly. In the total system, single first order DT_{50}s were 272-277 days. No metabolites were identified and none accounted for > 1% AR. Mineralisation was negligible (0.6-0.9% AR after 100 days) and bound residues reached maximum level of 15% AR at day 100.

FOCUS surface water modelling was evaluated up to step 4 for cereals scenarios with one and two applications of bromuconazole. Because of the persistence of the active substance in the water-sediment study ($DT_{90\ whole\ system}$ > 900 days) the applicant was asked to provide FOCUSsw modelling that takes into account the potential for accumulation in sediment as outlined in SANCO/4802/2001

section 8.7.3[5]. Additionally, the peer review requested further clarifications on the mitigations measures employed in step 4 calculations for runoff scenarios, as there is no agreed standardised way of implementing this reduction in FOCUSsw at EU level. The assumption used in step 4, together with calculations of the possible accumulation of bromuconazole in sediment for three scenarios were provided in the revised version of the DAR (June 2007) and discussed at the meeting of experts. The selected scenarios (D1, D4 and R4) were regarded as the worst case scenarios for PEC_{sed} calculations, but results for PEC_{water} values were not provided. It was noted that when drift mitigation with vegetative buffer strips are used in the modelling, the resulting driving forces for water body contamination are runoff and drainage. Therefore, depending on when the most important runoff event occurs, the PEC_{sed} values will be more or less sensitive to the soil DT_{50} used. Unfortunately, the experts considered this value (124.9 days from field studies) not applicable (see section 4.1.2); nevertheless, they agreed that at this stage the information provided is the best available on accumulation of bromuconazole in sediment. A data gap was identified for new FOCUSsw modelling to provide PEC_{sed} taking into account accumulation in sediment, using a more reliable soil DT_{50}. It was also concluded that, as the results considering only spray drift mitigation for the water column are still missing, new FOCUSsw modelling at step 3 and step 4 with spray drift mitigation only should be provided, taking into account a more reliable soil DT_{50} value when this data becomes available. Provisional PECs at step 3 calculated with the unacceptable soil DT_{50} of 124.9 days can be used for the risk assessment as it is likely that a longer soil DT_{50} value will not affect significantly the results. The agreed bromuconazole input parameters, other than soil DT_{50} were: K_foc= 757mL/g, 1/n=0.82, water SFO DT_{50}=277 days, sediment DT_{50}= 1000 days.

4.2.2. POTENTIAL FOR GROUND WATER CONTAMINATION OF THE ACTIVE SUBSTANCE THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

The leaching potential of bromuconazole to groundwater was estimated with FOCUS PEARL model and FOCUS scenarios for the applied for intended uses to winter cereals. One additional simulation was made with FOCUS MACRO model with the scenario of Châteaudun. However, as a consequence of the experts discussion regarding the identified data gap for new field soil dissipation studies (see section 4.1.2), a data gap was set for new PECgw calculations when new reliable field degradation values normalised to FOCUS reference conditions will become available.

4.3. FATE AND BEHAVIOUR IN AIR

Results from studies on volatilisation of bromuconazole from soil and bush beans indicated that volatilisation of the active substance is negligible 24 hours after application.

The vapour pressure of 0.4 x 10^{-5} Pa at 25ºC indicates that bromuconazole would be classified as non volatile. Calculations using the method of Atkinson for indirect photooxidation in the atmosphere through reaction with hydroxyl radicals were provided in the physical/chemical properties section of the DAR. Assuming an atmospheric concentration of 5 x 10^5 OH radical/cm^3 the estimated half life

[5] "FOCUS Surface Water Scenarios in the EU Evaluation Process under 91/414/EEC". Report of the FOCUS Working Group on Surface Water Scenarios, EC Document Reference SANCO/4802/2001-rev.2.

was 16.5 hrs or 1.4 d, indicating the small proportion of applied bromuconazole that will volatilise would be unlikely to be subject to long range atmospheric transport.

5. Ecotoxicology

Bromuconazole was discussed at the PRAPeR Expert's Meeting on ecotoxicology (PRAPeR 28) in July 2007. Bromuconazole belongs to the group of triazole fungicides which are suspected to have potential endocrine disrupting properties. No indication of endocrine disrupting effects on reproduction were found in the mammalian toxicity studies. No information was delivered to address this point with regard to potential effecs on birds and fish (e.g. a fish full life cycle test or a specific two generation study with birds). The meeting agreed that further information on birds and fish should be submitted by the applicant to address the concern with regard to endocrine disruption. A data requirement on the compliance assessment of the batches used in the ecotox tests with the technical specification was identified during the peer-review process. The applicant submitted further information on the specification of the material used in the ecotox studies. No evaluation on the compliance with the technical specification was conducted and hence the data requirement was kept open after the expert meeting. Currently no agreed technical specification is available. In the environmental risk assessment it was not considered that bromuconazole consists of 4 isomeres. This adds additional uncertainty to the outcome of the risk assessment and needs to be addressed further.

5.1. RISK TO TERRESTRIAL VERTEBRATES

The representative evaluated use of bromuconazole is as fungicide in wheat with a first application of 0.2 kg a.s./ha at BBCH 29-31 and a second application of 0.2 kg a.s./ha two months later corresponding to BBCH 49-51 in southern Europe and BBCH 59-65 in northern Europe. The risk to birds and mammals was assessed in accordance with the Guidance Document on Risk Assessment for Birds and Mammals (SANCO/4145/2000). The risk to birds was assessed for large herbivorous birds for the early application and to insectivorous birds for the late application. The TER values for herbivorous birds were above the Annex VI triggers (TER_a=172, TER_{st}=102, TER_{lt}=7.5) indicating a low risk. Also for insectivorous birds the TER values for acute and short term were well above the trigger (199 and 113) while the long-term TER of 4.4 was below the trigger of 5 indicating a potential high long-term risk. The RMS considered the long-term risk as addressed based on the argument that refinement of PT and PD would lead to a TER above the trigger of 5. However no further information/argumentation was provided to support a PT or PD refinement. The experts agreed that the risk needs to be addressed further and an open point was set for the RMS to conduct a refined long-term risk assessment for insectivorous birds. No new risk assessment was provided and a data gap is proposed by EFSA to address the long-term risk to insectivorous birds.

The risk to earthworm- and fish-eating birds was assessed as low. It was noted that the

The risk to mammals was assessed for small herbivorous mammals for the early application, and to insectivorous mammals for the late application. The acute TERs for herbivorous and insectivorous

mammals were above the trigger of 10 (including refinement of residues in plant material). The choice of the long-term endpoint was discussed in the expert meeting. The experts considered effects on bodyweight and bodyweight gain observed at the dose of 13.8 mg a.s./kg bw/d as relevant and suggested to use the next lower dose of 1.3 mg a.s/kg bw/d as the NOAEL to be used in the risk assessment. The updated risk assessment resulted in long-term TERs below the trigger of 5. Further refinement of the long-term risk to herbivorous, insectivorous and vermivorous mammals is necessary.
No major metabolites were found in the plant metabolism studies.

A risk assessment for uptake of contaminated drinking water was considered as not required for the suggested use in cereals.

5.2. RISK TO AQUATIC ORGANISMS

Based on the available acute toxicity data, bromuconazole is proposed to be classified as very toxic to aquatic organisms. The lowest end point value for technical bromuconazole was obtained for algae, with an EC_{50} of 0.061 mg a.s./L based on increase in biomass. Formulation studies were conducted with a SC formulation which was considered to be sufficiently similar to the lead formulation. The results did not indicate that the formulation would be more acutely toxic to fish and algae than expected from the content of bromocunazole. However the toxicity of formulated bromuconazole to daphnids was increased by about 2 orders of magnitude (acute EC_{50} = 0.083 mg a.s./L) and 1 order of magnitude (chronic NOEC = 0.0027 mg a.s./L), respectively.
The Annex VI trigger values of 100 and 10 were exceeded for fish, algae and higher aquatic plants in all FOCUSstep3 scenarios. The risk to aquatic invertebrates needed further refinement. The TERs were calculated with a 5m no-spray buffer zone for the drainage scenarios and a 10m no spray bufferzone including a vegetated filter strip to mitigate the run-off by 90%. The acute TERs (formulation endpoints) were above 100 in 4 full FOCUS drainage scenarios (D3, D4, D5, D6) out of 6 drainage scenarios and in all run-off scenarios. The chronic TERs were above the trigger of 10 in all scenarios except the part scenarios D1(ditch) and D2(ditch) based on endpoints from technical bromuconazole. Based on the chronic endpoint for the formulation no full FOCUS scenario exceeds the trigger of 10. The experts agreed that the formulation endpoints are of relevance for the entry into surface water via spray drift and that the risk assessment should be based on the lower formulation endpoints for those scenarios where spray drift contributes significantly to the PECsw. The applicant stated that the formulation tested with daphnids contains nonyl-phenol and that the representative formulation which will be marketed would be less toxic. The experts agreed to set a data gap for the applicant to submit a bridging study with daphnids and the new formulation.

However the PECsw values calculated in the DAR are not reliable and therefore the aquatic risk assessment can only be finalised once reliable PECsw values are available.

Bromuconazole partitions to sediment and is also persistent in the sediment. A risk assessment for *Chironomus riparius* based on the maximum PECsediment (87.57 µg bromuconazole/kg) resulted in

a TER above the trigger of 10. A 10m vegetated buffer strip was included in the calculation. The calculated PECsediment is not reliable (see section on fate and behaviour) and hence the risk assessment for sediment dwelling organisms needs to be finalised after reliable PECsediment values are established.

The bioconcentration factor was determined to be 131 for whole fish with a clearance half-life of 0.4 days. Hence the potential for bioaccumulation is considered as low.

No major metabolites were detected in the aerobic soil degradation studies or in the water/sediment studies that would pose a risk to aquatic organisms.

5.3. RISK TO BEES

Oral and contact toxicity of technical bromuconazole to bees is low. The hazard quotients are well below the Annex VI trigger indicating a low risk. No first tier studies with the formulation are available but a semi-field study with formulated bromuconazole did not show any acute toxic effects and only short-term effects on flight intensity. Therefore the risk to bees is considered to be low.

5.4. RISK TO OTHER ARTHROPOD SPECIES

Glass plate studies with the two indicator species, *Aphidius rhopalosiphi* and *Typhlodromus pyri* were conducted with the formulation EXP10064 E which is similar to the representative formulation Granit (the formulations differ only in the solvent). Mortality was 46% for *A. rhopalosiphi* and 93 % for *T. pyri* at an application rate corresponding to 250 g a.s./ha. Hence the in-field risk for *T. pyri* was considered to be high. Additional glass plate studies with *Coccinella* septempunctata (tested with EXP 10064E) and *Crysoperla carnea* (tested with the formulation EXP 100064A) using the same dose gave 60.9 % mortality for *C. septempunctata* and 23.4 % mortality for *C. carnea.* In an extended laboratory test with *C. septempunctata* no significant effects on mortality and no significant reduction in reproduction was observed at 239 g a.s./ha . No effects on mortality was observed at an application rate of 591 g bromocunazole/ha in a standard test with *Poecilius cupreus* using the formulation EXP 10592 A. An extended laboratory study with *T. pyri* and the formulation SCAE 0307 was submitted to address the potential high risk to predatory mites. The study was assessed in the addendum of June 2007. Effects of 38% mortality was observed at an initial dose rate of 250 g a.s./ha. The RMS concluded that the risk to non-target arthropods is sufficiently addressed. However it was pointed out in the expert meeting that the approach did not follow the ESCORT II scheme and that also an extended laboratory study with *A. rhopalosiphi* should be required. It was noted that no positive control was included in the test with *C carnea* and that increased reproduction was observed in the extended laboratory study with *C. septempunctata* at low doses which is considered a reaction induced by stress. Uncertainty remained with regard to the comparability of the different formulations used. Therefore a data gap was proposed during the expert meeting that studies with non-target arthropods and the formulation which is intended to be used should be submitted. It was argued by the applicant and the RMS that the formulations are sufficiently similar and that the formulation intended to be marketed will be SCAE 0307 which was used in the extended laboratory study with

predatory mites. EFSA agrees that the formulations are sufficiently similar to allow a comparison of the test results. Taking all information together EFSA agrees to the assessment of the RMS that the risk to non-target arthropods is likely to be low for the representative use evaluated. EFSA suggests that the data gap identified in the expert meeting should be addressed at MSs level for the formulation that is intended to be marketed.

5.5. RISK TO EARTHWORMS

The acute toxicity of bromuconazole to earthworms is low. The formulation 'EXP 10064 B/kg substrate, which was considered to be sufficiently similar to Granit, was more toxic than expected based on the concentration of bromocunazole. The risk assessment presented in the DAR were based on plateau maximum PEC_{soil} of 0.308 mg a.s./kg (acute) and the average plateau PEC_{soil} of 0.18 mg a.s./kg. The PECsoil values were rejected by the fate experts and as an interim PECsoil value it was proposed to base the risk assessment on a PECsoil of 0.832 mg/kg (see section on fate and behaviour). The resulting TER values would still be above the Annex VI trigger values.

5.6. RISK TO OTHER SOIL NON-TARGET MACRO-ORGANISMS

The formulation Granit had no significant effect on organic matter decomposition over a six months period in a litter bag test at an application rate of 180 g a.s./ha and 500 g a.s./ha. The soil concentration was calculated in the DAR as 0.67 mg a.s./ha. This concentration did not cover the interim PECplateau concentration of 0.832 mg a.s./kg soil and hence a data gap was identified in the expert meeting. The RMS commented in the evaluation table that the applicant informed them that the correct theoretical dose would be 0.907 mg/kg soil (in the upper 10cm) after application of 180 g a.s./ha and 500 g a.s./ha and hence would cover the interim PECsoil. It appears that the soil concentration calculated in the DAR was for the application rate of 500 g a.s./ha but did not include the rate of 180 g a.s./ha. EFSA agrees to the statement of the applicant and considers the risk to organic matter breakdown as sufficiently addressed by the available litterbag-study.

5.7. RISK TO SOIL NON-TARGET MICRO-ORGANISMS

Technical bromuconazole had no effects >25% after 28 days on soil respiration or nitrogen transformation at a soil concentration of 0.667 mg a.s./kg soil equivalent to an application rate of 500 g a.s./ha when compared to the control. The formulation Granit had no effects >25% on soil respiration and nitrogen transformation at a dose rate 8 times higher than the estimated maximum PEC_{soil} after 28 days in a sandy clay-loam soil. However nitrogen transformation was observed to be affected up to 41% in a clay-loam soil at the same dose rate and up to 28% at an application rate of 400 g a.s./ha (0.53 mg a.s./kg soil). However, the effect decreased to 17% at 60 days and to 15% at 90 days and to 10% and 4.2%, respectively. The tested concentrations of 0.667 mg a.s./kg soil and 0.53 mg a.s./kg soil do not cover the interim plateau PECsoil. Hence new studies are necessary to cover the peak PECsoil concentration.

5.8. RISK TO OTHER NON-TARGET-ORGANISMS (FLORA AND FAUNA)

No specific tests of effects on non-target plants were available in the DAR but a short summary of data/observations in non-cereal crops was given. No phytotoxic effects were reported but a growth regulatory response was observed in some cases. In order to confirm the absence of effects, the RMS required vegetative vigour and seedling emergence tests. The studies were summarized in the addendum of June 2007. The experts agreed to the risk assessment and concluded that the risk to non-target plants is low for the representative use evaluated.

5.9. RISK TO BIOLOGICAL METHODS OF SEWAGE TREATMENT

Data from an available test with technical bromuconazole gave an EC_{50} of >1000 mg a.s./L and a NOEC of 10 mg a.s./L for inhibition of respiration rate of activated sludge micro-organisms. It is not expected that bromuconazole will reach sewage treatment plants at concentrations of >10 mg a.s./L and hence the risk is considered to be low.

6. Residue definitions

Soil

Definitions for risk assessment: bromuconazole

Definitions for monitoring: bromuconazole

Water

Ground water

Definitions for exposure assessment: bromuconazole

Definitions for monitoring: bromuconazole

Surface water

Definitions for risk assessment: bromuconazole

Definitions for monitoring: bromuconazole

Air

Definitions for risk assessment: bromuconazole

Definitions for monitoring: bromuconazole

Food of plant origin

Definitions for risk assessment: PROVISONAL: bromuconazole (sum of isomers)

Definitions for monitoring: PROVISONAL: bromuconazole (sum of isomers)

Food of animal origin

Definitions for risk assessment: PROVISONAL: bromuconazole (sum of isomers)

Definitions for monitoring: PROVISONAL: bromuconazole (sum of isomers)

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

Soil

Compound (name and/or code)	**Persistence**	**Ecotoxicology**
bromuconazole	High to very high persistence Single first order $DT_{50\ lab}$ 329-1028 days (3 soils only; 20-22°C, 80% soil moisture capacity at 0.33 bar) Data gap identified for reliable field DT_{50} taking into account the influence of the photolytic degradation that is expected to occur at the soil surface.	The risk to earthworms and organic matter breakdown was assessed as low, the studies with soil micro-organisms do not cover the preliminary maximum accumulated peak PEC soil.
M04 (anaerobic soil degradation)	No data, not required.	No data available, no data required

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 relevance**
bromuconazole	Medium to low mobility K_{foc} 474-1539 mL/g	Data gap identified for new PECgw calculations when new reliable field degradation values will be available.	Yes	Yes	Yes

Surface water and sediment

Compound (name and/or code)	Ecotoxicology
bromuconazole	Bromuconazole is very toxic to aquatic organisms.

Air

Compound (name and/or code)	Toxicology
bromuconazole	Not acutely toxic via inhalation

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

- A revised technical specification is required (relevant for all uses evaluated, data gap identified by PRAPeR meeting of experts, date of submission unknown, refer to chapter 1).
- A dissociation constant study in accordance with OECD 112 (relevant for all uses evaluated, data gap identified by PRAPeR meeting of experts, date of submission unknown, refer to chapter 1).
- A metabolism study in cereals with the triazole label (relevant for all uses evaluated, data gap identified by PRAPeR meeting of experts, date of submission unknown, refer to section 3.1.1).
- A rotational crop metabolism study with the triazole label (relevant for all uses evaluated, data gap identified by PRAPeR meeting of experts, date of submission unknown, refer to section 3.1.2).
- The exposure of the consumer to triazole metabolites needs to be addressed for all areas (primary crops, rotational crops, animal matrices) (relevant for all uses evaluated, data gap identified by PRAPeR meeting of experts, date of submission unknown, refer to section 3).
- Adequate field dissipation studies are required to derive suitable estimates of microbial degradation for modelling purposes (relevant for all uses evaluated, data gap identified by PRAPeR meeting of experts, date of submission unknown, refer to section 4.1.2).
- Predicted environmental concentrations (PEC) in soil will need to be calculated when new reliable dissipation data will be available (relevant for all uses evaluated, data gap identified by PRAPeR meeting of experts, date of submission unknown, refer to section 4.1.2).
- New FOCUS SW modelling to provide PEC in sediment taking into account accumulation in sediment, using a more reliable soil DT_{50} value when these data will be available, is required (relevant for all uses evaluated, data gap identified by PRAPeR meeting of experts, date of submission unknown, refer to section 4.2.1).
- New FOCUS SW modelling at step 3 and step 4 with spray drift mitigation only and using a more reliable soil DT_{50} value when these data will be available, is required (relevant for all uses evaluated, data gap identified by PRAPeR meeting of experts, date of submission unknown, refer to section 4.2.1).
- New FOCUS GW modelling will need to be performed when reliable biodegradation rate under field conditions will become available (relevant for all uses evaluated, data gap identified by PRAPeR meeting of experts, date of submission unknown, refer to section 4.2.2).
- Bromuconazole consists of 4 isomers. This needs to be taken into account in the environmental risk assessment. Information on the toxicity and/or on the degradation of the 4 isomers in the environment is needed. (relevant for all representative uses evaluated; open point identified after the expert meeting; no submission date proposed by the applicant; refer to section 5).

- The potential risk of endocrine disrupting effects should be addressed for birds and fish (relevant for all representative uses evaluated; data gap identified in the meeting expert (PRAPeR 28 in July 2007); no submission date proposed by the applicant; refer to point 5).
- The long-term risk assessment for birds needs refinement. (relevant for all representative uses evaluated; open point identified during the peer-review and suggested as a data gap by EFSA after the expert meeting; no submission date proposed by the applicant; refer to point 5.1.
- Further refinement of the long-term risk to herbivorous, insectivorous and vermivorous mammals is necessary. (relevant for all representative uses evaluated; data gap identified by the RMS and confirmed by EFSA after the expert meeting; no submission date proposed by the applicant; refer to point 5.1.
- A bridging study with daphnids and the new formulation is necessary. (relevant for all representative uses evaluated; data gap identified in the expert meeting (PRAPeR 28 in July 2007); no submission date proposed by the applicant; refer to point 5.2.
- The aquatic risk assessment needs to be finalised once reliable PECsw values are established (relevant for all representative uses evaluated; data gap identified after the expert meeting (PRAPeR 28 in July 2007); no submission date proposed by the applicant; refer to point 5.2.
- New studies on soil micro-organisms covering the maximum plateau PECsoil (relevant for all representative uses evaluated; data gap identified after the expert meeting (PRAPeR 28 in July 2007); no submission date proposed by the applicant; refer to point 5.7).

CONCLUSIONS AND RECOMMENDATIONS

Overall conclusions

The conclusion was reached on the basis of the evaluation of the representative uses as a fungicide on wheat full details of the gap can be found in the attached list of end points.

The representative formulated product for the evaluation was "EXP10064C", a suspension concentrate formulation (SC).

Adequate methods are available to monitor all compounds given in the respective residue definition. Residues in food of plant origin can be determined with a multi-method (The German S19 method has been validated). For the other matrices only single methods are available to determine residues of bromuconazole.

Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection product are possible. The remaining issues are that the technical specification can not be finalised and there is a data gap identified for a dissociation constant study.

In mammals, bromuconazole oral LD_{50} is 328 mg/kg bw (classification as “harmful if swallowed” (Xn; R22), proposed). The acute toxicity by dermal and inhalation route is low (LD_{50}>2000 mg/kg bw and LC_{50}>5 mg/L). Bromuconazole is neither skin nor eye irritant. It is not a skin sensitiser.

In repeated dose toxicity studies, the liver is the target organ. In subchronic tests, the dog is the most sensitive species, with an overall relevant NOAEL of 2.5 mg/kg bw/day whereas in rat the NOAEL is 13.8 mg/kg bw/day. In genotoxicity testing there was some indication of weak clastogenicity *in vitro*, however there was no indication of positive results were *in vivo*, neither in the micronucleus assay nor in the UDS assay. Overall, bromuconazole was considered devoid of genotoxic potential.
The relevant NOAEL for long term toxicity and carcinogenicity in rat is 0.88 mg/kg bw/day: treatment-related neoplastic lesions in rodents occurred at high doses: hepatocellular and cholangiocellular carcinomas in rats and hepatocellular carcinoma in mice. In both rats and mice, the tumours were likely caused by liver toxicity and subsequent cell renewal. Overall, it was agreed that bromuconazole does not have carcinogenic potential relevant to humans. Bromuconazole did not show any reproductive toxicity potential: parental and foetal toxicity NOAELs were established at 1.3 mg/kg bw/day, while the reproductive NOAEL was established at 141 mg/kg bw/day. As for developmental toxicity, in the rat the relevant maternal NOAEL is 70 mg/kg bw/day, whereas the developmental NOAEL is 10 mg/kg bw/day, based on a dose-dependent increase of placental weight and ossification delays or supernumerary bones in a number of skeletal structures. It was agreed to propose classification Cat 3, Xn; R63, 'May cause harm to unborn child'. The ADI of 0.01 mg/kg bw/day was set based on the relevant long term toxicity/carcinogenicity NOAEL of 0.88 mg/kg bw/day from the 2 year rat study, applying an SF of 100. For the ARfD, the value is based on the developmental NOAEL of 10 mg/kg bw/day from the rat study, with an SF of 100, leading to an ARfD of 0.1 mg/kg bw. The AOEL of 0.025 mg/kg bw/day was set on basis of the NOAEL of 2.5 mg/kg bw/day from the 90-day dog study (applying a standard SF of 100). The operator exposure showed exposure levels below the AOEL (15.6%) with the application of the German model and the use of gloves during mixing/loading and application and coveralls and sturdy footwear during application. The estimated exposure for re-entry activities (scouting) is 1.5% of the AOEL. The bystander exposure is estimated to be 1.6% of the AOEL.

The metabolism of bromuconazole was investigated in wheat (relevant to the notified use). Additional metabolism data was submitted for the category of fruit crops. A metabolic pathway could be established in cereals. At harvest, bromuconazole was still a major part of the terminal residue in cereal matrices and identified metabolites were individually below 10% of the total residue. However, there was indication of preferential metabolism of one bromuconazole diastereomer (LS 850647), as a significant shift in the ratio of diastereomers was found in the residues determined in the mature cereal crop when compared to the ratio in the initially applied bromuconazole. Whether the ratio of enantiomers in each diastereomer was subject to any shift was not investigated.
In rotational crops studies there was uptake of residues from soil into succeeding cereal, oilseed, root and leafy crops. Upon analysis of the residues the two bromuconazole diastereomers were identified as major residue, and similar to the primary cereal metabolism their ratio had been shifted compared to the one in the bromuconazole applied to the soil. No information is available on the ratio of enantiomers in each diastereomer.
The submitted livestock metabolism data in ruminants and poultry allows to establish a metabolic pathway, and suggests that no residues in food of animal origin above the limit of quantification are

expected when cereals treated according the cGAP are used in livestock diet. The data implies that there might be preferential metabolism of one diastereomers also in livestock animals. The ratio of enantiomers in each diastereomer was not investigated.
As plant and livestock residue data indicate that from the notified use no significant consumer exposure to bromuconazole residues is expected, the observed shift of the isomer ratio in the terminal residue is currently not a concern with regard to consumer safety. This may have to be reconsidered when authorisation of uses is sought that lead to consumer exposure to bromuconazole residues above the limit of quantification.
The meeting of experts noted that all studies were performed using phenyl-labelled bromuconazole only, and thus the fate of the triazole moiety of the molecule was not investigated. The experts agreed that based on the available data and information cleavage of the molecule cannot be excluded and further investigation of the triazole moiety is required to address potential consumer exposure to triazole derivative metabolites. Until then, the plant and animal residue definition is provisional, and consequently the consumer risk assessment is not finalised.

The information available on the fate and behaviour in the environment was not adequate to carry out an appropriate environmental exposure assessment at the EU level. Aerobic soil metabolism and degradation studies performed in the laboratory suggested that bromuconazole is high to very high persistent in soil. Nevertheless, satisfactory field dissipations studies that enable determination of reliable biodegradation rates for bromuconazole were identified as being necessary for modelling purposes. As a consequence, new PECsoil, and PECgw calculations will need to be calculated using a more reliable soil DT_{50}. In addition, a sound conclusion on the surface water exposure assessment at higher tier (step 4) could not be reached for the FOCUS scenarios. New FOCUS SW modelling to provide PEC_{sed} values taking into consideration the accumulation of bromuconazole in sediment will be also necessary.

The long-term TER for insectivorous birds was 4.4 indicating a potential high long-term risk. The RMS considered the long-term risk as addressed based on the argument that refinement of PT and PD would lead to a TER above the trigger of 5. However no further information/argumentation was provided to support a PT or PD refinement. The experts agreed that the risk needs to be addressed further and an open point was set for the RMS to conduct a refined long-term risk assessment for insectivorous birds. No new risk assessment was provided and a data gap is proposed by EFSA to address the long-term risk to insectivorous birds. The risk to mammals was assessed for small herbivorous mammals for the early application, and to insectivorous mammals for the late application. The acute TERs for herbivorous and insectivorous mammals were above the trigger of 10 (including refinement of residues in plant material). The choice of the long-term endpoint was discussed in the expert meeting. The experts considered effects on bodyweight and bodyweight gain observed at the dose of 13.8 mg a.s./kg bw/d as relevant and suggested to use the next lower dose of 1.3 mg a.s/kg bw/d as the NOAEL in the risk assessment. The updated risk assessment resulted in long-term TERs below the trigger of 5. Further refinement of the long-term risk to herbivorous, insectivorous and vermivorous mammals is necessary. Bromuconazole is very toxic to aquatic

organisms. A potential high risk was indicated in with FOCUS step3 PECsw values. The available information suggests that substantial risk mitigation measures would be required to meet the Annex VI triggers. No agreed reliable PECsw values are currently available to conclude on the risk to aquatic organisms. The risk assessment for non-target arthropods was not in accordance to the ESCORT II scheme. The standard glass plate tests suggest that there will be some adverse effects on sensitive non-target arthropods. Extended lab studies gave an indication that the risk to non-target arthropods is low. Concerns were raised with regard to the comparability of the different formulations used in the studies with non-target arthropods. EFSA agrees to the assessment of the RMS that the formulations are sufficiently similar to conclude on the risk to non-target arthropods for the representative use. The applicant informed that a different formulation than Granit will be marketed. It is suggested that a risk assessment for this formulation is conducted at MSs level after the decision on Annex I inclusion. The formulation Granit had no significant effect on organic matter decomposition over a six months period in a litter bag test at an application rate of 180 g a.s./ha and 500 g a.s./ha. The soil concentration was calculated in the DAR as 0.67 mg a.s./ha. This concentration does not cover the interim PECplateau concentration of 0.832 mg a.s./kg soil and hence a data gap was identified in the expert meeting. However it was noted after the expert meeting that the theoretical soil concentration in the litterbag-study was calculated for an application rate of 500 g a.s./ha only but should also include the rate of 180 g a.s./ha. The recalculated theoretical soil concentration of 0.907 mg/kg soil would cover the interim PECplateau concentration and hence no new litterbag-study is required. Effects of >25% on nitrogen transformation were observed at an application rate of 400 g a.s./ha (0.53 mg a.s./kg soil) at day 28 but fell below 25% within 100 days. The tested concentration of 0.53 mg a.s./kg soil does not cover the interim plateau PECsoil. A potential high risk to soil micro-organisms cannot be excluded and new studies are necessary to cover the peak PECsoil concentration.

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

- Use of PPE has to be considered to reduce estimated exposure levels below the AOEL (refer to point 2.12)

Critical areas of concern

- The technical specification has not been finalised.
- The consumer risk assessment with regard to the triazole metabolites cannot be finalised due to lack of data.
- The surface water exposure assessment has not been finalised.
- The groundwater exposure assessment has not been finalised.
- The long-term risk assessment for insectivorous birds needs further refinement
- Further refinement of the long-term risk to herbivorous, insectivorous and vermivorous mammals is necessary.
- Bromuconazole is very toxic to aquatic organisms and the risk assessment is not finalised.
- The studies with soil micro organisms do not cover the peak PECsoil concentrations and effects of >25% on soil nitrification were observed after 28 days.

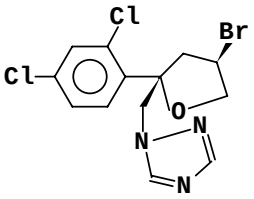
APPENDIX 1 – LIST OF ENDPOINTS FOR THE ACTIVE SUBSTANCE AND THE REPRESENTATIVE FORMULATION

(Abbreviations used in this list are explained in appendix 2)

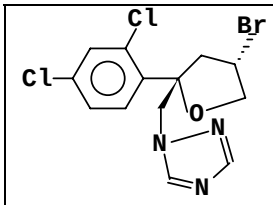
Appendix 1.1 Identity, Physical and Chemical Properties, Details of Uses, Further Information

Active substance (ISO Common Name) ‡	Bromuconazole
Function (*e.g.* fungicide)	Fungicide
Rapporteur Member State	Belgium

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	1-[(2*RS*,4*RS*:2*RS*,4*SR*)-4-bromo-2-(2,4-dichlorophenyl)tetrahydrofurfuryl]-1*H*-1,2,4-triazole
Chemical name (CA) ‡	1-[[4-bromo-2-(2,4-dichlorophenyl)tetrahydro-2-furanyl]methyl]-1H-1,2,4-triazole
CIPAC No ‡	680
CAS No ‡	116255-48-2
EC No (EINECS or ELINCS) ‡	408-060-3
FAO Specification (including year of publication)‡	No FAO specification available.
Minimum purity of the active substance as manufactured (g/kg) ‡	Min. 960 g/kg Bromuconazole (LS850646 + LS850647), with LS850646 ranging between 500 to 560 g/kg and LS850647 ranging between 420 to 480 g/kg. These ranges imply ratios LS850646/LS850647 between 1.04:1 and 1.33:1
Identity of relevant impurities (of toxicological, environmental and/or other significance) in the active substance as manufactured (g/kg)	None
Molecular formula ‡	$C_{13}H_{12}BrCl_2N_3O$
Molecular mass ‡	377.1 g/mol
Structural formula ‡	Bromuconazole is a mixture of two diastereomeric pairs of enantiomers (LS850646 and LS850647)  **LS850646** ± (2RS,4SR)

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles



LS850647
± (2RS,4RS)

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Physical-chemical properties (Annex IIA, point 2)

Melting point (state purity) ‡	84°C (98.9%, DSC) (LS 850646 + LS 850647) 92 ± 1 °C (98.8%, capillary tube in liquid bath) (LS 850646 + LS 850647) 91°C (99.5%, DSC) (LS850646) 101°C (99.9%, DSC) (LS850647)
Boiling point (state purity) ‡	Not applicable (decomposition)
Temperature of decomposition (state purity)	194°C (98.9%)
Appearance (state purity) ‡	white to beige powder, slightly alcoholic odour (96.8%) beige powder, no characteristic odour (98.2%)
Vapour pressure (state temperature, state purity) ‡	0.4 x 10^{-5} Pa at 25°C (98.3%) (LS 850646 + LS 850647) 0.3 x 10^{-5} Pa (LS 850646) at 25°C 0.1 x 10^{-5} Pa (LS 850647) at 25°C
Henry's law constant (Pa m^3 mol^{-1}) ‡	1.05 x 10^{-5} Pa.m³.mol^{-1} at 20°C (LS850646) 1.57 x 10^{-5} Pa.m³.mol^{-1} at 20°C (LS850647)
Solubility in water (state temperature, state purity and pH) ‡	distilled water, 20°C : 49 mg/L LS850646 + 24 mg/L LS850647 (100%) distilled water, 20°C : 72 mg/L (LS850646, 100%) distilled water, 20°C : 24 mg/L (LS850647, 99.7%)
	No effect of pH (97.4%)
Solubility in organic solvents (state temperature, state purity) ‡	

	at 20°C in g/L (97.4%)	
	LS850646	LS850647
n-hexane	1.65	1.92
toluene	217.2	156.8
dichloromethane	499.7	353.7
methanol	295.4	188.5
1-octanol	61.4	38.5
2-propanol	57.4	39.8
acetone	318.6	219.7
ethylacetate	231.9	173.0

Surface tension (state concentration and temperature, state purity) ‡	59.8 mN/m at 21°C (90% saturated solution) (98.8%) Concentrations of diastereoisomers in test solution: LS850646: 5.74 x 10^{-2} g/L; LS850647: 1.83 x 10^{-2} g/L
Partition co-efficient (log P_{OW}) (state pH and temperature) ‡	distilled water, 20°C, 98.9% pure log P_{ow} = 3.24 (LS 850646 + LS 850647) log P_{ow} = 3.12 (LS 850646) log P_{ow} = 3.48 (LS 850647)
	Effect of pH does not need to be addressed (molecule will not be ionized at environmentally relevant pH values)
Dissociation constant (state purity) ‡	Bromuconazole is estimated to have 2 equilibria : pKa_I = + 2.75 ± 0.1 pKa_{II} = - 4.02 ± 0.3

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

	This indicates that neutral Bromuconazole is the only species present at environmental pH. *Data gap: test (OECD 112) required*
UV/VIS absorption (max.) incl. ε (state purity, pH) ‡	*LS850646 (99.9%):* λ_{max} (nm) / ε (L.mol^{-1}.cm^{-1}) Aqueous solutions (with 1% methanol) acidic: 204.0 / 38527; 220.0* / 11157 neutral: 202.5 / 43936; 220.0* / 10762 basic: 221.5 / 9915 Methanol solutions 205.0 / 21534; 220.0* / 6790 at λ 295 nm / 0.49 *LS850647 (*99.3%*) :* λ_{max} (nm) / ε (L.mol^{-1}.cm^{-1}) Aqueous solutions (with 1% methanol) acidic: 204.0 / 36614; 221.0* / 10611 neutral: 203.0 / 42091; 220.0* / 10329 basic: 220.5 / 9560 Methanol solutions 206.0 / 22705; 220.0* / 8205 at λ 295 nm / 2.27 * shoulder *The photolysis study, which provided different UV/VIS spectra, is in question.*
Flammability (state purity) ‡	not highly flammable (98.8%) not auto-flammable (98.8%)
Explosive properties (state purity) ‡	not explosive (98.8%)
Oxidising properties (state purity) ‡	not oxidising (98.8%)

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Summary of representative uses evaluated (bromuconazole)

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 a.s. (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hl min max	water l/ha min max	kg as/ha min max		
Wheat	Europe	EXP 10064C	F	*Tapesia* spp. *Mycosphaerella graminicola* *Stagonospora nodorum* *Puccinia recondita* *Puccinia striiformis* *Blumeria graminis* f.sp. *tritici* *Fusarium* spp	SC	200 g/l	spraying	BBCH 29-31 BBCH 49-51 (S.E) 59-65 (N.E.)	1 1	c.a. 2 months	0.050-0.100 0.050-0.100	200-400 200-400	0.200 0.200		[1] [2]

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

[1] Data gaps and potential high risks were identified in section 5 (ecotoxicology). The long-term risk to birds and mammals needs further refinement. The aquatic risk assessment is not finalised. A potential high risk was identified for soil micro-organisms.
[2] The consumer risk assessment is not finalised due to lack of data.

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 suckling 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,
(h) drench
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 Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(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

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.2 Methods of Analysis

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

Technical as (analytical technique)	HPLC-UV (method B-488-06-91(E)) no CIPAC method available
Impurities in technical as (analytical technique)	HPLC-UV (method B-590-07-91(E)); GC-FID (method B-591-04-91(E)); Karl Fischer
Plant protection product (analytical technique)	HPLC-UV (method B-706-01-93(E)) or GC-FID (method AM004404MF1) no CIPAC method available

Analytical methods for residues (Annex IIA, point 4.2)

Residue definitions for monitoring purposes

Food of plant origin		Bromuconazole (sum of isomers) Provisional
Food of animal origin		Bromuconazole (sum of isomers) Provisional
Soil		Bromuconazole (sum of isomers)
Water	surface	Bromuconazole (sum of isomers)
	drinking/ground	Bromuconazole (sum of isomers)
Air		Bromuconazole (sum of isomers)

Monitoring/Enforcement methods

Food/feed of plant origin (analytical technique and LOQ for methods for monitoring purposes)	Multi method DFG S19 (modified) : GC-ECD, conf. by column of different polarity or GC/MSD (Bromuconazole); LOQ = 0.05 mg/kg (cereals)
Food/feed of animal origin (analytical technique and LOQ for methods for monitoring purposes)	Single method AR 120-96 : GC-ECD, conf. by GC-MSD (Bromuconazole); LOQ = 0.01 mg/kg (milk), 0.02 mg/kg (beef meat, egg, bovine liver, bovine kidney, bovine fat)
Soil (analytical technique and LOQ)	Single method AR 71-89 (E) : GC-ECD, conf. by column of different polarity (Bromuconazole); LOQ = 0.02 mg/kg
Water (analytical technique and LOQ)	Single method AR 74-89 (E) : GC-ECD, conf. by GC-MSD (Bromuconazole); LOQ = 0.1 µg/L (surface water, drinking water)
Air (analytical technique and LOQ)	Single method : LC/MS/MS (Bromuconazole); LOQ = 0.4 µg/m³
Body fluids and tissues (analytical technique and LOQ)	Not required (active substance is not classified as toxic or highly toxic)

Classification and proposed labelling (Annex IIA, point 10)

with regard to physical/chemical data	none

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.3 Impact on Human and Animal Health

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

Rate and extent of absorption ‡	Rapid (<48h) and almost complete (88%) based on urinary and bile excretion.
Distribution ‡	Widely distributed; slight preference for liver, kidney, adrenales and blood
Potential for accumulation‡	None
Rate and extent of excretion ‡	Rapid, within 48h: 88-97%.
Metabolism in animals ‡	Extensive phase I metabolisation (hydroxylation) of the tetrahydrofurane and dichlorobenzene ring, followed by glucuronide or sulphate conjugation. Glucuronide or amino acid conjugation of triazole ring. No evidence of phenyl-, THF- or triazole ring degradates (only THF ring opening).
Toxicologically significant compounds (animals, plants and environment) ‡	Bromuconazole , TA , TAA and 1,2, 4- triazole.

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral ‡	328 (♀) mg/kg b.w. ***(Xn; R22)***
Rat LD_{50} dermal ‡	>2000 mg/kg b.w.
Rat LC_{50} inhalation ‡	>5 mg/L air (micronised dust, 4h- nose only)
Skin irritation ‡	Not irritant
Eye irritation ‡	Not irritant
Skin sensitization (test method , result) ‡	Maximisation test, no sensitisation

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect ‡	90d/1yr dog: liver weight increase, increased alkaline phosphatase and transaminase activity, adrenal cortical vacuolation
Lowest relevant oral NOAEL / NOEL ‡	2.5 mg/kg b.w./day (90- day and 1-year dog) 13.8 mg/kg bw/day (90-day, rat)
Lowest relevant dermal NOAEL / NOEL ‡	500 mg/kg b.w./day (21-day, rat)
Lowest relevant inhalation NOAEL / NOEL ‡	Not available, not required

Genotoxicity (Annex IIA, point 5.4) ‡	*In-vitro:* negative bacterial, equivocal mammalian genotoxicity; weak clastogenicity (CA in CHO cells and human lymphocytes) *In-vivo:* negative in UDS and BM micronucleus Overall, no genotoxic potential.

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

Target/critical effect ‡	Liver (rat, mouse)
Lowest relevant NOAEL / NOEL ‡	0.88-1.09 mg/kg b.w./day (2 yr- rat) 2.27 mg/kg b.w./day (80 weeks mouse)
Carcinogenicity ‡	Hepatocellular carcinoma (rat, mouse) and

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

	cholangiocarcinoma (rat) at high dose level producing marked hepatoxicity (87.2 mg/kg bw/day in rat, 370 mg/kg bw/day in mouse). Overall, no carcinogenic potential relevant ot human exposure levels.

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction target / critical effect ‡	•parents: ↓body weight gain, ↑liver weight, hepatocyte fatty vacuolation •pups: ↓body weight gain (F2) No adverse reproductive effects.
Lowest relevant reproductive NOAEL / NOEL ‡	•NOAEL parental: 1.3 mg/kg b.w./day •NOAEL pups: 1.3 mg/kg b.w./day •NOAEL reprotox: 141 mg/kg b.w./day (highest dose)
Developmental target / critical effect ‡	Rat (maternal): ↓b.w. gain, ↑water consumption, ↑liver weight Rat :↑placental weight Rat (developmental): ↑7th cervical ribs, domed head and anophtalmia at high dose ***(Xn, R63)***
	Rabbit maternal: Decreased bw gain, clinical signs Rabbit developmental: Increased of visceral and skeletal variant.
Lowest relevant developmental NOAEL / NOEL ‡	•Rat NOAEL maternal: 70 mg/kg b.w./day •Rat NOAEL developmental: 10 mg/kg b.w./day
	Rabbit NOAEL maternal: 12.5 mg/kg b.w./day Rabbit NOAEL developmental: 12.5 mg/kg bw/day

Neurotoxicity / Delayed neurotoxicity (Annex IIA, point 5.7) ‡

(i) Delayed neurotoxicity: (ii) Acute and subchronic neurotoxicity	No data, not required No data, not required

Other toxicological studies (Annex IIA, point 5.8) ‡

(i) Potential effect of Bromuconazole on porphyria (dog, 29d capsule feeding) (ii) Acute toxicity, bacterial genotoxicity and/or chromosome aberration studies on metabolite LS860364 and impurities (RPA 400063, RPA 400064, LS880225, LS880226, RPA405516, RPA405517)	(i) erythema or gum reddening observed in subchronic dog studies not replicated in mechanistic study, hence no porphyria detected. (ii) Metabolite or impurities not more acutely toxic than Bromuconazole, devoid of genotoxic potential

Medical data (Annex IIA, point 5.9) ‡

Based on the reports of the medical surveillance on manufacturing plant personnel, no effects were related to the exposure to the a.s.

Summary (Annex IIA, point 5.10)	Value	Study	Safety factor
ADI ‡	0.01	2-year rat	100
AOEL ‡	0.025	90-day and 1-year dog	100
ARfD (acute reference dose) ‡	0.10	developmental rat	100

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Dermal absorption (Annex IIIA, point 7.3) ‡

In-vivo penetration study (rat) Granit EXP 10064	Low dose: 5%; High dose: 45%

Acceptable exposure scenarios (including method of calculation)

Operator	Application to cereals : UK POEM (% of AOEL) (tractor, 200 g a.s./ha, without PPE) 1317% (tractor, 60 g.a.s./ha, PPE = gloves during mixing/loading plus application) 201% BBA (% of AOEL) (tractor, 200 g a.s./ha, without PPE) 238% (tractor, 200 g a.s./ha, PPE = gloves during mixing/loading) 15%
Workers	According to Hoernicke et al. 1998: <4.5% of AOEL (with PPE)
Bystanders	According to Ganzelmeier 1995: <1.6% of AOEL

Classification and proposed labelling (Annex IIA, point 10)

with regard to toxicological data	Xn; R22 ('Harmful by oral uptake') Xn; R63 ('May cause harm to unborn child')

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.5 Residues

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

Plant groups covered	Cereals (wheat)[6]
Rotational crops	Cereals (spring/winter wheat), Root and tuber vegetables (radish), Leafy vegetables (lettuce) [7]
Metabolism in rotational crops similar to metabolism in primary crops?	Yes
Processed commodities	No data available – none required
Residue pattern in processed commodities similar to residue pattern in raw commodities?	Not applicable
Plant residue definition for monitoring	Provisional: [#] Bromuconazole (sum of isomers)
Plant residue definition for risk assessment	Provisional: [#] Bromuconazole (sum of isomers)
Conversion factor (monitoring to risk assessment)	None

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

Animals covered	Lactating cows and goats Laying hens
Time needed to reach a plateau concentration in milk and eggs	Milk 1-2 days Eggs 4-5 days
Animal residue definition for monitoring	Provisional: [#] Bromuconazole (sum of isomers)
Animal residue definition for risk assessment	Provisional: [#] Bromuconazole (sum of isomers)
Conversion factor (monitoring to risk assessment)	None
Metabolism in rat and ruminant similar (yes/no)	Open [8]
Fat soluble residue: (yes/no)	Yes (Log $P_{O/W}$ = 3.24)

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

Rotational crop studies showed that levels of bromuconazole in succeeding crops are not likely to exceed the enforcement LOQ of 0.05 mg/kg. This conclusion is provisional and will need to be reconsidered regarding the triazole derivative metabolites.[9]

[6] Data gap for a cereal metabolism study with triazole labelling
[7] Data gap for a rotational crop study with triazole labelling
[#] This residue definition is provisional and will need to be reconsidered regarding the triazole derivative metabolites upon submission of data addressing the identified data gaps.
[8] Inconclusive with regard to triazole derivative metabolites.

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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

Wheat (grain and straw)	Stable for 20 months at -18°C

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

Note: The estimates refer only to livestock intakes of bromuconazole. Potential intakes and residue levels of triazole derivative metabolites in animals will have to be assessed separately.

	Ruminant:	Poultry:	Pig:
	Conditions of requirement of feeding studies		
Expected intakes by livestock ≥ 0.1 mg/kg diet (dry weight basis) (yes/no - If yes, specify the level)	yes dairy cattle 0.49 mg/kg DM beef cattle 1.2 mg/kg DM	no	no
Potential for accumulation (yes/no):	yes	n/a	n/a
Metabolism studies indicate potential level of residues ≥ 0.01 mg/kg in edible tissues (yes/no)	no	n/a	n/a
	Feeding studies (Specify the feeding rate in cattle and poultry studies considered as relevant) Residue levels in matrices [10]: Mean (max) mg/kg		
Muscle	<0.02	n/a	n/a
Liver	<0.02	n/a	n/a
Kidney	<0.02	n/a	n/a
Fat	<0.02	n/a	n/a
Milk	<0.01		
Eggs		n/a	

[9] Data gap for a rotational crop study with triazole labelling
[10] No feeding study submitted. Estimated on the basis of the available metabolism studies bromuconazole residues are not likely to exceed the LOQ of the proposed monitoring method.

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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)
Wheat	N	Grain: 3 x <0.01; 9 x <0.02; 2 x <0.025; 1 x <0.021; 8 x <0.05 Straw: 0.06; 0.13; 0.16; 0.41; 0.51; 0.55; 0.78; 0.93; 0.93; 0.98; 1.0; 1.2; 1.2; 1.3; 1.5	Since all residues in grains are below the enforcement LOQ of 0.05 mg/kg (multi-method), it is proposed to set the MRL at 0.05*mg/kg	0.05*	0.05 1.5	0.02 0.93
Wheat	S	Grain: 3 x <0.01; 4 x <0.02; 1 x <0.025 Straw: 0.086; 2x 0.14; 0.19; 0.24; 0.46; 0.57; 1.0	Since all residues in grains are below the enforcement LOQ of 0.05 mg/kg (multi-method), it is proposed to set the MRL at 0.05*mg/kg	0.05*	0.025 1.0	0.02 0.22

(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

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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

Note: This consumer risk assessment is provisional and will have to be reconsidered regarding potential intake of triazole derivative metabolites.

ADI	0.01 mg/kg bw
TMDI (% ADI) according to WHO European diet	2.3 %
TMDI (% ADI) according to national (to be specified) diets	3.7 % (German model) 4 % and 14 % respectively for children and infants (UK long term exposure model).
IEDI (WHO European Diet) (% ADI)	Not required.
NEDI (specify diet) (% ADI)	Not required.
Factors included in IEDI and NEDI	Not applicable.
ARfD	0.10 mg/kg bw/d
IESTI (% ARfD)	Wheat: 0.3 % (General population WHO consumption data) 0.5 % (Children WHO consumption data) Milk: 0.3 % (General population WHO consumption data) 0.8 % (Children WHO consumption data) Meat: 0.2 % (General population WHO consumption data) 0.3 % (Children WHO consumption data) Liver: 0.1 % (General population WHO consumption data) 0.2 % (Children WHO consumption data) Kidney: 0.2 % (General population WHO consumption data) 0.3 % (Children WHO consumption data)
NESTI (% ARfD) according to national (to be specified) large portion consumption data	Not assessed.
Factors included in IESTI and NESTI	None.

Processing factors (Annex IIA, point 6.5, Annex IIIA, point 8.4)

Crop/ process/ processed product	Number of studies	Processing factors		Amount transferred (%) (Optional)
		Transfer factor	Yield factor	
No data submitted – none required	n/a	n/a	n/a	n/a

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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

Note: Proposals are relevant to the provisional monitoring residue definition, i.e. to bromuconazole, sum of isomers, only.

Wheat grain	0.05* mg/kg
Milk	0.01* mg/kg
Ruminant meat	0.02* mg/kg
Ruminant fat	0.02* mg/kg
Ruminant liver	0.02* mg/kg
Ruminant kidney	0.02* mg/kg

* LOQ

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.5 Fate and Behaviour in the Environment

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

Mineralization after 100 days ‡	1.3-4.4 % AR after 120 d, [^{14}C-phenyl]-label (n= 2)
Non-extractable residues after 100 days ‡	10.2-17.6 % AR after 120 d, [^{14}C-phenyl]-label (n= 2)
Relevant metabolites - name and/or code, % of applied (range and maximum) ‡	None

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

Anaerobic degradation ‡	No mineralization non-extractable residues: 15% AR after 90 days 2-(2,4-dichlorophenyl-2-(1,2,4-triazol-1-yl methyl)) tetrahydrofuran (LS 871387): 10% AR after 181 days [^{14}C-phenyl]-label
Soil photolysis ‡	Mineralisation: 0.6% AR after 30 days non-extractable residues: 14.7% AR after 30 days SFO DT50 irradiated : 78 days, summer sunlight 50° N no major metabolite [14C-phenyl]-label

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

Method of calculation	Laboratory: non linear single first order kinetics
Laboratory studies (range or median, with n value, with r^2 value) ‡	DT_{50lab} (20-22°C, aerobic): 329-1028 d (n=3, χ^2 error = 1.9-5.9)
	DT_{90lab} (20-22°C, aerobic): 1091-3414 d (n=3, χ^2 error = 1.9-5.9)
	DT_{50lab} (10°C, aerobic): 609-1826 d (n= 2, χ^2 error = 1.8-2.1)
	DT_{50lab} (22°C, anaerobic): 356 d (n= 1, χ^2 error = 5.4)
	degradation in the saturated zone: ‡ not required
Field studies (state location, range or median with n value) ‡	No acceptable data available, data gap.
Soil accumulation and plateau concentration ‡	Accumulation factors calculated in the study UK site: 2.56 DE site: no plateau reached.

Soil adsorption/desorption (Annex IIA, point 7.1.2)

K_f /K_{oc} ‡	K_{oc} isomer LS850646: 474-1086 mL / g (mean 757 mL / g , $^1/_n$= 0.78-0.85, 4 soils) K_{oc} isomer LS850647: 627-1539 mL / g (mean 987 mL / g , $^1/_n$= 0.76-0.86, 4 soils)
K_d ‡	
pH dependence (yes / no) (if yes type of	

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

dependence) ‡	K_f: isomer LS850646: 4.5-26.5 mL / g (mean 10.5 mL / g , 4 soils) K_f: isomer LS850647: 5.0-37.5 mL / g (mean 14.5 mL / g, 4 soils) No dependence with pH *For FOCUS gw modelling – K_{oc}: parent, mean 757 mL/g, $^1/_n$=-0.82

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

Column leaching ‡	Guideline: 'not stated' Time period (d): not given Precipitation (mm): 508 mm Leachate: 0.2-0.6% total residues/radioactivity in leachate; the leachate contains predominantly the a.s. 62.4-97.6 % total residues/radioactivity retained in top 6 cm
Aged residues leaching ‡	Guideline: 'not stated' Aged for (d): 210 d Time period (d): not given Precipitation (mm): 508 mm Leachate: 1.8-2.4 % total residues/radioactivity in leachate; the leachate contains predominantly the a.s. 69.5-101.9 % total residues/radioactivity retained in top 6 cm
	Guideline: 'UK MAFF' Aged for (d): 210 d Time period (d): not given Precipitation (mm): 508 mm Leachate: 2.0-3.1 % total residues/radioactivity in leachate; the leachate contains 4 unidentified polar compounds. 86.8-90.3% total residues/radioactivity retained in top 6 cm
Lysimeter/ field leaching studies ‡	Not required

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

PEC (soil) (Annex IIIA, point 9.1.3)

Parent

Method of calculation	No acceptable data available, data gap.

PECsoil, accumulation

Provisional PEC soil from accumulation field studies	0.832 mg a.s. / kg soil

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

Hydrolysis of active substance and relevant metabolites (DT_{50}) (state pH and temperature) ‡	
	pH 4, 25°C : DT_{50} > 30 d (LS850646, > 98%; LS850647, > 98%)
	pH 5, 25°C : DT_{50} > 30 d (LS850646, > 98%; LS850647, > 98%)
	pH 7, 25°C : DT_{50} > 30 d (LS850646, > 98%; LS850647, > 98%)
	pH 9, 25°C : DT_{50} > 30 d (LS850646, > 98%; LS850647, > 98%)
Photolytic degradation of active substance and relevant metabolites ‡	No photodegradation of Bromuconazole at 25°C in the environmentally relevant pH 9
Readily biodegradable (yes/no) ‡	Not readily biodegradable
Degradation in water/sediment - DT_{50} water ‡	2.0-1.3 d
- DT_{90} water ‡	235-53.8 d (multicompartment 1st order, r^2= 0.97-0.99, n= 2)
- DT_{50} whole system ‡	272-277 d
- DT_{90} whole system ‡	903-921 d (1st order, r^2= 0.98-0.94, n= 2)
Mineralization	0.6-0.9 %AR (at 100 d, study end, n= 2)
Non-extractable residues	15.3-15.1 %AR (at 100 d, study end, n= 2)
Distribution in water / sediment systems (active substance) ‡	Maximum of 63.0-70.4%AR in sediment after 61 days.
Distribution in water / sediment systems (metabolites) ‡	No major metabolite

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

Parent

Method of calculation	Data gap identified at PRAPeR 27 Provisional results at Step 3 can be found at pp. 8-49 and 8-50 of the revised DAR (January 2008). In these calculations a soil DT_{50} = 124.9 days, derived from field studies, was not considered acceptable by the experts.

PEC (ground water) (Annex IIIA, point 9.2.1)

No acceptable data available, data gap

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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

Direct photolysis in air ‡	Not required
Quantum yield of direct phototransformation	Not required
Photochemical oxidative degradation in air ‡	estimated half life in atmosphere = 16.5 hr or 1.4 d (Atkinson calculation using global OH-concentration of 5.0 x 10^5 OH radicals/cm^3 and 12 hours irradiation per day)
Volatilization ‡	from plant surfaces: a.s. volatilization is negligible 24 hours after application
	from soil: a.s. volatilization is negligible 24 hours after application

PEC (air)

Method of calculation	Not required

$PEC_{(a)}$

Maximum concentration	Not required

Definition of the Residue (Annex IIA, point 7.3)

Relevant to the environment	Soil: bromuconazole Water (GW and SW): bromuconazole Sediment: bromuconazole Air: bromuconazole

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

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

Classification and proposed labelling (Annex IIA, point 10)

with regard to fate and behaviour data	Candidate for R53

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.6 Effects on Non-target Species

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 ‡				
Anas platyrhynchos	bromuconazole	Acute	> 2150	-
Colinus virginianus	bromuconazole	Acute	> 2150	-
Anas platyrhynchos	bromuconazole	Short-term	> 684	> 5000
Colinus virginianus	bromuconazole	Short-term	> 778	> 5000
Coturnix coturnix japonica	bromuconazole	Long-term	26.5	250
Mammals ‡				
Female rat	bromuconazole	Acute	328	-
Rat	bromuconazole	Long-term	1.3	-
Additional higher tier studies ‡				
Not required.				

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

Wheat, 2 x 0.200 kg a.s./ha

Indicator species/Category[2]	Time scale	ETE	TER[1]	Annex VI Trigger[3]
Tier 1 (Birds)				
Large herbivorous bird (early)	Acute	12.5	172	10
	Short-term	6.67	102	10
	Long-term	3.54	7.5	5
Insectivorous bird (early/late)	Acute	10.8	199	10
	Short-term	6.03	113	10
	Long-term	6.03	4.4	5
Earthworm-eating bird	Long-term	0.298	24.1	5
Fish-eating bird	Long-term	0.085	312	5
Higher tier refinement (Birds)				
By weight of evidence the long-term risk for insectivorous birds was considered acceptable. The use of realistic estimates of the exposure scenario (refined RUD, PT and PD) will lead to a higher TER value than 4.4 and thus an acceptable long-term risk.				
Tier 1 (Mammals)				
Small herbivorous mammal (early)	Acute	39.5	8.31	10
	Long-term	11.2	0.12	5

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Indicator species/Category[2]	Time scale	ETE	TER[1]	Annex VI Trigger[3]
Insectivorous mammal (late)	Acute	1.76	186	10
	Long-term	0.64	2.03	5
Earthworm-eating mammal	Long-term	0.379	0.93	5
Fish-eating mammal	Long-term	0.053	24.5	5
Higher tier refinement (Mammals)				
Small herbivorous mammal (early)	Acute	4.03 (residues)	81.4	10
	Long-term	2.14 (residues)	0.61	5

[1] in higher tier refinement provide brief details of any refinements used (e.g., residues, PT, PD or AV)
[2] for cereals indicate if it is early or late crop stage
[3] If the Annex VI Trigger value has been adjusted during the risk assessment of the active substance (e.g. many single species data), it should appear in this column.

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	bromuconazole	96 h (flow-through)	Mortality, LC_{50}	1.7 mg a.s./L (mm)
Lepomis macrochirus	bromuconazole	96 h (flow-through)	Mortality, LC_{50}	3.1 mg a.s./L (mm)
Oncorhynchus mykiss	bromuconazole	21 d (flow-through)	Growth, NOEC	0.21 mg a.s./L (mm)
Pimephales promelas	bromuconazole	35 d (flow-through)	Growth, NOEC	0.065 mg a.s./L (mm)
Oncorhynchus mykiss	EXP 10064 B	96 h (semi-static)	Mortality, EC_{50}	14 mg form/L (2.69 mg a.s./L) (nom)
Oncorhynchus mykiss	EXP 10064 B	21 d (semi-static)	Growth, NOEC	0.56 mg form/L (0.11 mg a.s./L) (nom)
Aquatic invertebrate				
Daphnia magna	bromuconazole	48 h (flow-through)	Mortality, EC_{50}	**> 8.9 mg a.s./L** (mm)
Daphnia magna	bromuconazole	21 d (semi-static)	Reproduction, NOEC	**0.020 mg a.s./L** (mm)

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Group	Test substance	Time-scale (Test type)	End point	Toxicity[1] (mg/L)
Daphnia magna	EXP 10064 B	48 h (static)	Mortality, EC_{50}	0.43 mg form/L (**0.083 mg a.s./L**) (nom)
Daphnia magna	EXP 10064 B	21 d (semi-static)	Reproduction, NOEC	0.0056 mg form/L (**0.0027 mg a.s./L**) (nom)
Sediment dwelling organisms				
Chironomus riparius	bromuconazole	28 d (static) sediment-water	NOEC	**0.250 mg a.s./L** (nom) **3.125 mg a.s./kg** (nom)
Algae				
Pseudokirchneriella subcapitata	bromuconazole	96 h (static)	Biomass: E_bC_{50} (72 h) Growth rate: E_rC_{50} (72 h)	> 3.3 mg a.s./L (nom) > 3.3 mg a.s./L (nom)
Pseudokirchneriella subcapitata	bromuconazole	120 h (static)	Biomass: E_bC_{50} (72 h) Growth rate: E_rC_{50} (72 h)	0.061 mg a.s./L (mm) 0.169 mg a.s./L (mm)
Anabaena flos-aquae	bromuconazole	120 h (static)	Biomass: E_bC_{50} (72 h) Growth rate: E_rC_{50} (72 h)	0.395 mg a.s./L (mm) 5.99 mg a.s./L (mm)
Pseudokirchneriella subcapitata	EXP 10064 B	120 h (static)	Biomass: E_bC_{50} (120 h) Growth rate: E_rC_{50} (24 h)	8.3 mg form/L (1.59 mg a.s./L) (nom) 15 mg form/L (2.88 mg a.s./L) (nom)
Higher plant				
Lemna gibba	bromuconazole	14 d (static)	Fronds, EC_{50}	0.12 mg a.s./L (initially measured)
Microcosm or mesocosm tests				
Not required. Acceptable representative uses are shown for the majority of the FOCUS scenarios. However, risk mitigation measures are recommended at Member State level to reduce the chronic risk to *Daphnia magna*.				

[1] indicate whether based on nominal ($_{nom}$) or mean measured concentrations ($_{mm}$). In the case of preparations indicate whether end points are presented as units of preparation or a.s.

EXP 10064 B : SC formulation containing 197.8 g/L bromuconazole (batch n° : OP 901120)

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

FOCUS Step1

FOCUS Step 2

Refined aquatic risk assessment using higher tier FOCUS modelling.

FOCUS Step 3

FOCUS Step 4

Crop and application rate : wheat, 1 x 0.200 kg a.s./ha
Crop and application rate : wheat, 2 x 0.200 kg a.s./ha

The aquatic risk assessment needs to be finalised once reliable PECsw values are available. Data gaps identified at PRAPeR 27 and PRAPeR 28

Bioconcentration				
	bromuco-nazole	Meta-bolite 1	Meta-bolite 2	Meta-bolite 3
$logP_{O/W}$	3.24	-	-	-
Bioconcentration factor (BCF)[1] ‡	* 131 (whole fish)	-	-	-
Annex VI Trigger for the bioconcentration factor	100	-	-	-
Clearance time (days) (CT_{50})	0.401 (whole fish)	-	-	-
(CT_{90})	1.332 (whole fish)	-	-	-
Level and nature of residues (%) in organisms after the 14 day depuration phase	3 % residues in whole fish after 21 d depuration, glucuronide conjugates of a hydroxylated derivate of bromuconazole	-	-	-

[1] only required if log $P_{O/W}$ >3.
* based on total ^{14}C

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)
bromuconazole ‡	> 100 µg a.s./bee	> 500 µg a.s./bee
Field or semi-field tests		
Higher tier testing is not necessary, since the hazard quotients of bromuconazole for oral and contact toxicity are below 50. However, acceptable cage studies were conducted. Application of the test substance Granit on a crop of flowering *Phacelia* in a flight cage resulted in different effects on the honeybee in both replications. In the 1st replication only a short-term decrease of flight intensity was observed after application of the test substance. In the 2nd replication the mortality in the test substance cage after application was slightly higher than in the water treated control variant. However, no acute intoxication was noted. According to the results obtained in this study Granit can be rated as harmless to bees.		

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Test substance	Acute oral toxicity (LD_{50} µg/bee)	Acute contact toxicity (LD_{50} µg/bee)
Two additional cage studies were submitted by the notifier. The references are Stute (1991) and Schultz (1992). These studies are comparable with the former cage studies, although not much detail is given. In the first study (Stute, 1991) the application rate was 2.0 L Granit in 200 L water/ha for each of the two applications. The tent size was 12 m² and the crop was *Phacelia*. The application caused no perturbation of foraging behaviour. No increased mortality or adverse effects on bee-brood were seen. In the second study (Schultz, 1992) the application rate was 1.0 L Granit in 200–400 L water/ha for each of the two applications. The tent size was 12 m² and the crop was *Phacelia*. A slight increase in mortality was observed at the end of the observation period after the second application.		

[1] for preparations indicate whether end point is expressed in units of a.s. or preparation

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

Crop and application rate : wheat, 2 x 0.200 kg a.s./ha

Test substance	Route	Hazard quotient	Annex VI Trigger
bromuconazole	contact	2	50
	oral	0.4	50

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

Laboratory tests with standard sensitive species
No such tests were performed.

Further laboratory and extended laboratory studies ‡

Species	Life stage	Test substance, substrate and duration	Dose (g a.s./ ha)[1,2]	Endpoint	% effect[3]	Trigger value
Laboratory tests						
Aphidius rhopalosiphi	adults	EXP 10064 E, glass plates, 48 h + 10 d	13 g a.s./ha, initial	Corrected mortality Reproduction	20.0 % + 1.2 %	50 % 50 %
			260 g a.s./ha, initial	Corrected mortality Reproduction	45.7 % + 74.4 %	50 % 50 %
Typhlodromus pyri	proto-nymphs	EXP 10064 E, glass plates, 7 d + 7 d	13 g a.s./ha, initial	Corrected mortality Reproduction	9.41 % - 6.2 %	50 % 50 %
			260 g a.s./ha, initial	Corrected mortality Reproduction	92.94 % -	50 % 50 %
Poecilus cupreus	adults	EXP 10592 A, sand, 14 d	591 g a.s./ha, initial	Corrected mortality Food consumption	0.0 % - 6.5 %	50 % 50 %
Coccinella septempunc-	larvae	EXP 10064 E, glass plates,	13 g a.s./ha, initial	Corrected mortality Reproduction	6.5 % - 67.7 %	50 % 50 %

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Species	Life stage	Test substance, substrate and duration	Dose (g a.s./ ha)[1,2]	Endpoint	% effect[3]	Trigger value
tata		16 – 27 d	260 g a.s./ha, initial	Corrected mortality Reproduction	60.9 % + 278 %	50 % 50 %
Chrysoperla carnea	larvae	EXP 10064 A, glass plates, 2 - 3 weeks	200 g a.s./ha	Corrected mortality Reproduction	23.4 % + 2.8 %	50 % 50 %
Extended laboratory tests						
Coccinella septempunc-tata	larvae	Granit, bean leaves, 14 d	11.94 g a.s./ha, initial	Corrected mortality Reproduction	- 5.4 % - 61.7 %	50 % 50 %
			119 g a.s./ha, initial	Corrected mortality Reproduction	- 2.7 % - 93.6 %	50 % 50 %
			191 g a.s./ha, initial	Corrected mortality Reproduction	- 8.1 % - 66.0 %	50 % 50 %
			239 g a.s./ha, initial	Corrected mortality Reproduction	- 2.7 % + 19.1 %	50 % 50 %
Typhlodromus pyri	proto-nymphs	Bromucona-zole SC, bean leaves, 14 d	15.625 g a.s./ha, initial	Corrected mortality Reproduction	4 % - 22.5 %	50 % 50 %
			31.25 g a.s./ha, initial	Corrected mortality Reproduction	12 % + 11.3 %	50 % 50 %
			62.5 g a.s./ha, initial	Corrected mortality Reproduction	13 % - 12.3 %	50 % 50 %
			125 g a.s./ha, initial	Corrected mortality Reproduction	17 % - 38.0 %	50 % 50 %
			250 g a.s./ha, initial	Corrected mortality Reproduction	38 % - 25.4 %	50 % 50 %

[1] indicate whether initial or aged residues
[2] for preparations indicate whether dose is expressed in units of a.s. or preparation
[3] indicate if positive percentages relate to adverse effects or not

Corrected mortality : positive values : adverse effects
Reproduction : negative values : adverse effects; positive values : no adverse effects
Food consumption : negative values : adverse effects; positive values : no adverse effects

EXP 10064 E : SC formulation containing 208 g/L bromuconazole (batch n° : OP 980605)
EXP 10592 A : EC formulation containing 197 g/L bromuconazole (batch n° : OP 940695)
EXP 10064 A : SC formulation containing 200 g/L bromuconazole (batch n° : OP 891015)
Granit (AE F125581 00 SC19 A 102) : SC formulation containing 191 g/L bromuconazole (batch n° : OP 220689)

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Field or semi-field tests
Not required. Laboratory and extended laboratory tests are available and no higher tier testing is 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[1]
Earthworms			
Eisenia foetida	bromuconazole ‡	acute	LC_{50} > 1000 mg a.s./kg soil dw LC_{50corr} > 500 mg a.s./kg soil dw
Eisenia foetida	EXP 10064 B	acute	LC_{50} = 1180 mg form/kg soil dw LC_{50corr} = 590 form/kg soil dw LC_{50corr} = 117 mg a.s./kg soil dw
Eisenia foetida	bromuconazole ‡	chronic	NOEC = 37.2 mg a.s./kg soil dw $NOEC_{corr}$ = 18.6 mg a.s./kg soil dw
Other soil macro-organisms			
Not required. A litterbag test was performed.			
Collembola			
Not required.			
Soil micro-organisms			
Nitrogen mineralisation	bromuconazole ‡	28 d	- 2.0 % effect at day 28 at 500 g a.s./ha, equivalent to 0.667 mg a.s./kg soil dw
	Granit	28 d (soil 1) 90 d (soil 2)	+ 20 % effect at day 28 at 2.0 kg a.s./ha, equivalent to 2.6 mg a.s./kg soil dw in sandy-clay loam (soil 1) - 15 % effect at day 90 at 2.0 kg a.s./ha, equivalent to 2.6 mg a.s./kg soil dw in clay loam (soil 2)
Carbon mineralisation	bromuconazole ‡	28 d	3.9 % effect at day 28 at 500 g a.s./ha, equivalent to 0.667 mg a.s./kg soil dw
	Granit	28 d (soil 1 and soil 2)	+ 2.4 % effect at day 28 at 2.0 kg a.s./ha, equivalent to 2.6 mg a.s./kg soil dw in sandy-clay loam (soil 1) - 7.5 % effect at day 28 at 2.0 kg a.s./ha, equivalent to 2.6 mg a.s./kg soil dw in clay loam (soil 2)
Field studies[2]			

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Test organism	Test substance	Time scale	End point[1]
A litterbag test was conducted. The application of 500 g bromuconazole/ha (as formulation Granit), equivalent to 0.67 mg a.s./kg soil, to straw had no significant adverse effect on organic matter decomposition under the tested field conditions over a 6 months post treatment period. This covers the plateau maximum PEC_{soil} at 20 cm soil depth of 0.077 mg a.s./kg soil.			

[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

EXP 10064 B : SC formulation containing 197.8 g/L bromuconazole (batch n° : OP 901120)

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Toxicity/exposure ratios for soil organisms

Wheat, 2 x 0.200 kg a.s./ha

Test organism	Test substance	Time scale	PEC_{soil} [2] (mg a.s./kg soil dw)	TER	Trigger
Earthworms					
Eisenia foetida	bromuconazole ‡	acute	0.832	>601	10
Eisenia foetida	EXP 10064 B	acute	0.832	141	10
Eisenia foetida	bromuconazole ‡	chronic	0.832	22.4	5

[1] to be completed where first Tier triggers are breached
[2] indicate which PEC soil was used (e.g. plateau PEC)

EXP 10064 B : SC formulation containing 197.8 g/L bromuconazole (batch n° : OP 901120)

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

Preliminary screening data

Effects of bromuconazole on non-target plants have never been evaluated in specific trials. Hov bromuconazole has been intensively tested in non cereal crops over a number of years in a range of Eur countries : winter rape, sunflower, field peas, sugar beet, potato, carrot, and to a small extent top fruits and vine

In winter rape, the crop safety was good in all trials at 200-250 g a.s./ha with 1 or 2 spring applications coveri beginning of stem elongation/pods formation growth stages. No plant growth regulator effect was found with treatments.
In sunflower, no adverse effects were seen at 250 g a.s./ha after 2 applications in all situations with th treatment done at capitul emergence.
In field peas, the selectivity at 200-250 g a.s./ha was always excellent with 2 applications, the first one starting flowering.
In sugar beet, bromuconazole demonstrated a regulator effect on the development of the plants. Shorteni petioles and limbs, greener colour and more waffled aspect of the leaves were often observed after 1 applicat 200 g a.s./ha. An increase of the sugar content and a better extractability rate were also generally observed b the other hand the root yield was reduced.
In potato, greener leaves were observed after 2-3 applications at 200-400 g a.s./ha with short spray intervals 12 days.
In carrot, no phytotoxicity was seen at 200-400 g a.s./ha with 2-4 sprays at 10-14 day intervals.
In top/stone fruits, bromuconazole was safe in all situations when used at 30-50 g a.s./ha. However, exc numbers of applications and higher dose rates sometimes resulted in a plant growth response (shortened inter in apple trees.
In vines, bromuconazole was generally selective at 20 g a.s./ha. However, a plant growth regulator response t to ergosterol biosynthesis inhibitor fungicides occurred occasionally. Effects were limited to a slight thickenir greening of leaves and tightening of bunches, they were variety dependant (caution should be taken with Carig

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Laboratory dose response tests

Most sensitive species	Test substance	ER_{50} (L form/ha)[2] vegetative vigour	ER_{50} (L form/ha)[2] emergence	Exposure[1] (L form/ha)[2]	TER	Trigger
All tested species	Granit Enerpar SC 200	> 1 L form/ha	-	0.025	40	5
corn, oats, oilseed rape, sunflower, soybean	Granit Enerpar SC 200	-	> 1 L form/ha	0.025	40	5
tomato	Granit Enerpar SC 200	-	0.616 L form/ha	0.025	24.6	5

1 explanation of how exposure has been estimated should be provided (e.g. based on Ganzelmeier drift data)
2 for preparations indicate whether dose is expressed in units of a.s. or preparation

Ganzelmeier drift values : 90th percentile drift value for 2 applications at 1 m : 2.38 %

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

Test type/organism	End point
Activated sludge	EC_{50} (30 min) > 1000 mg a.s./L EC_{50} (3 h) > 1000 mg a.s./L
Pseudomonas sp	-

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

Compartment	
soil	bromuconazole
water	bromuconazole
sediment	bromuconazole
groundwater	bromuconazole

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

	RMS/peer review proposal
Active substance	N, R50

	RMS/peer review proposal
Preparation	N, R50

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

APPENDIX 2 – ABBREVIATIONS USED IN THE LIST OF ENDPOINTS

ADI	acceptable daily intake
AOEL	acceptable operator exposure level
ARfD	acute reference dose
a.s.	active substance
bw	body weight
CA	Chemical Abstract
CAS	Chemical Abstract Service
CIPAC	Collaborative International Pesticide Analytical Council Limited
d	day
DAR	draft assessment report
DM	dry matter
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
ε	decadic molar extinction coefficient
EC_{50}	effective concentration
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINKS	European List of New Chemical Substances
EMDI	estimated maximum daily intake
ER50	emergence rate, median
EU	European Union
FAO	Food and Agriculture Organisation of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	good agricultural practice
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GS	growth stage
h	hour(s)
ha	hectare
hL	hectolitre
HPLC	high pressure liquid chromatography or high performance liquid chromatography
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
K_{oc}	organic carbon adsorption coefficient
L	litre
LC	liquid chromatography
LC-MS	liquid chromatography-mass spectrometry
LC-MS-MS	liquid chromatography with tandem mass spectrometry

LC_{50}	lethal concentration, median
LD_{50}	lethal dose, median; dosis letalis media
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification (determination)
µg	microgram
mN	milli-Newton
MRL	maximum residue limit or level
MS	mass spectrometry
NESTI	national estimated short term intake
NIR	near-infrared-(spectroscopy)
nm	nanometer
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
PEC	predicted environmental concentration
PEC_A	predicted environmental concentration in air
PEC_S	predicted environmental concentration in soil
PEC_{SW}	predicted environmental concentration in surface water
PEC_{GW}	predicted environmental concentration in ground water
PHI	pre-harvest interval
pK_a	negative logarithm (to the base 10) of the dissociation constant
PPE	personal protective equipment
ppm	parts per million (10^{-6})
ppp	plant protection product
r^2	coefficient of determination
RPE	respiratory protective equipment
STMR	supervised trials median residue
TER	toxicity exposure ratio
TMDI	theoretical maximum daily intake
UV	ultraviolet
WHO	World Health Organisation
WG	water dispersible granule
yr	year

APPENDIX 3 – USED COMPOUND CODE(S)

Code/Trivial name	Chemical name	Structural formula
LS860364	1-[2-(2,4-dichlorophenyl)-2,5-dihydrofuran-2-ylmethyl]-1H-1,2,4-triazole