CONCLUSION ON PESTICIDE PEER REVIEW

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

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SUMMARY

Triazoxide is one of the 84 substances of the third stage Part B of the review programme covered by Commission Regulation (EC) No 1490/2002[3], as amended by Commission Regulation (EC) No 1095/2007[4]. 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.

The United Kingdom being the designated rapporteur Member State submitted the DAR on triazoxide in accordance with the provisions of Article 10(1) of the Regulation (EC) No 1490/2002, which was received by the EFSA on 25 June 2007. Following a quality check on the DAR, the peer review was initiated on 4 October 2007 by dispatching the DAR to the sole applicant Bayer CropScience AG, and on 5 November 2007 to the Member States for consultation. Subsequently, the comments received on the DAR were examined and responded by the rapporteur Member State in the reporting table. This table was evaluated by EFSA to identify the remaining issues. The identified issues as well as further information made available by the notifier upon request were evaluated in a series of scientific meetings with Member State experts in May – June 2008.

A final discussion of the outcome of the consultation of experts took place during a written procedure with the Member States in August 2008 leading to the conclusions as set out in the EFSA Conclusion finalised on 30 September 2008 (EFSA Scientific Report (2008) 193).

Following the Commission Decision of 30 November 2009 (2009/860/EC)[5] concerning the non-inclusion of triazoxide in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing that substance, the applicant Bayer CropScience AG made a resubmission application for the inclusion of triazoxide in Annex I in accordance with the provisions laid down in Chapter III of Commission Regulation (EC) No. 33/2008[6]. The resubmission dossier included further data in response to the issues identified in the conclusions leading to the Decision on non-inclusion, as set out in the Review Report (SANCO/216/08 – rev. 0) as follows:

- the information available was insufficient to satisfy the requirements set out in Annex II and Annex III of Directive 91/414/EEC, in particular with regard to:

[1] On request from the European Commission, Question No EFSA-Q-2010-01058, issued on 15 February 2011.

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

[4] OJ L 246, 21.9.2007, p. 19

[5] OJ L 314, 01.12.2009, p.81

[6] OJ L 15, 18.01.2008, p.5

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- the available metabolism and residue data were not considered appropriate to conduct a robust consumer risk assessment due to the uncertainties identified with regard to the nature of residues in plant commodities and the possible transfer of residues in animal products
- the long-term risk for granivorous birds
- the long-term risk for granivorous mammals
- the long-term risk to fish
- the long-term risk to earthworms

- and concerns were identified with regard to:

  - the consumer exposure

In accordance with Article 18 of Commission Regulation (EC) No. 33/2008, the United Kingdom, being the designated RMS in the resubmission procedure, submitted an evaluation of the additional data in the format of an Additional Report. The Additional Report was received by the EFSA on 10 June 2010.

In accordance with Article 19 of Commission Regulation (EC) No. 33/2008, the EFSA distributed the Additional Report to Member States and the applicant for comments on 16 June 2010. The EFSA collated and forwarded all comments received to the Commission on 30 July 2010.

In accordance with Article 20, following consideration of the Additional Report and the comments received, the Commission requested the EFSA to conduct a focussed peer review in the area of mammalian toxicology and deliver its conclusions on triazoxide.

The conclusion from the original review was reached on the basis of the evaluation of the representative uses as a fungicide as proposed by the applicant, which comprise seed treatment in barley against several agriculturally important diseases. The conclusions of the resubmission were reached on the basis of the evaluation of the same representative uses. Full details of the representative uses can be found in Appendix A to this report.

Data gaps were identified in the section on identity and analytical methods. The specification for the technical material should currently be regarded as provisional.

The representative formulated product for the evaluation was 'Raxil S FS 040', a flowable concentrate for seed treatment (FS), containing 20 g/L triazoxide and 20 g/L tebuconazole.

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. Adequate methods are available to monitor all compounds given in the respective residue definition in food/feed of plant origin, soil and water, however for air a method validated to a LOQ of 0.3 µg a.s./m³ was identified as a data gap.

With regard to its toxicological properties, triazoxide was rapidly and extensively absorbed, but only partly bioavailable (50 %) to the target organ (blood system) due to its biokinetic properties. After single exposure it was shown to be toxic after oral or inhalative administration, but was not irritant or skin sensitizer. Consequently, the proposed classification for acute toxicity was **T, R23/25 'Toxic by inhalation and if swallowed'**.

After repeated oral or inhalative administration, the critical effect was the induction of haemolytic anaemia, with secondary effects in the spleen, liver, kidneys and bone marrow. The possible classification with Xn; R48/22 or T; R48/25 ('Harmful or Toxic: danger of serious damage to health by prolonged exposure if swallowed') could not be agreed by the experts, but the classification **T, R48/23 'Toxic: danger of serious damage to health by prolonged exposure through inhalation'** was proposed. Triazoxide did not show genotoxic or carcinogenic properties in the available studies.

No specific adverse effects on fertility were observed in the multi-generation rat study, but the classification **R64 'May cause harm to breastfed babies'** was proposed based on reduced pup survival during lactation that could be expected to result from the presence of triazoxide in milk. No developmental toxicity or teratogenic activity was observed in rats or rabbits.

The **acceptable daily intake** (ADI) is **0.0002 mg/kg bw/day,** based on the 2-year rat study and using a safety factor of 100, increased by an additional safety factor of 3. This was justified by the use of a lowest observed adverse effect level, the steep dose-response in the study and the absence of mechanistic information. The **acceptable operator exposure level** (AOEL) is **0.001 mg/kg bw/day,** based on the 90-day rat study, using a safety factor of 100 and a correction for bioavailability (50 %). The **acute reference dose** (ARfD) is **0.015 mg/kg bw,** based on the 4-week rat study and applying a safety factor of 100.

The dermal absorption values to be used in the risk assessment are 2.4 % for the concentrate and 2 % for the contaminated grain dust. The operator exposure estimates during the seed treatment are above the AOEL with the SeedTropex model, but realistic field studies show an exposure level up to 21 % of the AOEL with the use of coverall and gloves. Similarly, the exposure estimates for the worker loading and sowing treated seed are above the AOEL with the SeedTropex model, but below the AOEL considering a field study (26 %), with the use of long-sleeved shirt and long trousers. Bystander exposure is not expected to exceed the exposure of workers involved in loading/sowing treated seed (i.e. 26 % of the AOEL).

Based on the new metabolism study conducted on barley with seeds treated at dose rates of 3 and 30 g a.s./100 kg seeds (N and 10N studies when compared to the critical GAP), the residue was defined as triazoxide alone for monitoring and as sum of triazoxide, desoxy-triazoxide (M01) and triazoxide-amino (M02) for risk assessment. A conversion factor of 6 was proposed for risk assessment derived from the metabolism study, taking into account the respective percentage at which each compound was detected in straw.

A new residue data set was submitted where samples were analysed using an analytical method achieving a LOQ of 0.001 mg/kg, and the MRL for barley grain was proposed at the LOQ value. Such an unusually low value was proposed, given the low ADI agreed for the parent compound. The residue data are supported by the storage stability study showing triazoxide residues to be stable up to 2 years when stored frozen at -18°C. Processing studies were not submitted and are not required. The available data are sufficient to conclude that significant residues are not expected to be present in rotational crops.

Estimated intakes by animals were calculated to be below the trigger value of 0.1 mg/kg DM. A goat metabolism study was however provided in order to confirm that transfer of residues in animal matrices is not expected at levels that could be of concern for the consumers. Since the total radioactive residues (TRRs) in goat matrices were shown to be below 0.0005 mg/kg when expressed on a 1N rate basis, the setting of a residue definition and proposing MRLs for animal matrices were considered not necessary.

No chronic or acute risks were identified for the consumers, with the TMDI being less that 4 % of the ADI and the IESTI less that 0.1 % of the ARfD when calculations are performed using the EFSA PRIMo model, the proposed MRL of 0.001 mg/kg for barley, and the conversion factor of 6.

Triazoxide may be considered to be highly to very highly persistent in soil under dark aerobic conditions at 20°C ($DT_{50\ lab\ (biphasic\ kinetic,\ overall)}$ = 208 – 278 days). The degradation of triazoxide proceeds either through reduction to M01, or through production of M02. The assessment based on the decline from the peak observed indicated that metabolite M01 was moderately persistent in soil ($DissT_{50\ lab}$ = 32.4 – 56.7 days), and metabolite M02 could be considered highly persistent (decline M02 $DissT_{50\ field}$ = 239 – 313 days; excluding the UK field trial where no decline is observed).

Unextracted residues amounted to a maximum of 29.8 % AR after 120 days (end of the study). Mineralization was practically negligible in the four soils tested.

Photolysis slightly enhances degradation of triazoxide in soil, but it is not expected to contribute significantly to its environmental dissipation.

According to the available studies, triazoxide may be considered as low to medium mobile in soil (K_{foc} = 245 – 1743 mL /g), metabolite M01 may be considered slightly mobile (K_{foc} = 2053 – 4148 mL /g), and metabolite M02 may be considered low to medium mobile (K_{foc} = 385.6 – 1709.0 mL /g). The narrow range of pH and the ionisable character of the metabolite M02 were noted. Whereas a large margin of safety is considered to exist for the representative use, further data could be needed if other uses at significantly higher application rates are applied for in the future.

Triazoxide was stable to hydrolysis at pH 4, practically stable at pH 7, and readily hydrolysed at pH 9 (DT_{50} = 6.6 days). The main hydrolysis metabolite was M04. Triazoxide is rapidly photolysed in water (DT_{50} = 24.4 hours equivalent to 3.5 natural solar days at 33 ºN). An additional study indicated that the photolysis half-life of triazoxide in water is expected to range from 1.7 to 9.7 days, depending on the season and the latitude (30 – 50 ºN).

No ready biodegradability study is available and therefore triazoxide is considered not readily biodegradable.

In aquatic water / sediment systems, triazoxide dissipated rapidly from water to sediment phase, and broke down to form the metabolites M01 and M05. Unextractable residues in the sediment amounted up to 55.7 % AR in the sediment after 91 days). Mineralization was negligible in both systems. The limited sampling regime of these experiments prevents the calculation of reliable kinetic parameters. However, a simple non-linear kinetic analysis was presented by the applicant to derive dissipation and degradation rates of triazoxide and metabolite M01 in the water sediment systems. This kinetic analysis was only partially validated (only whole system results for the Lienden system were confirmed). For the IJzendoorn system, no reliable whole system half-lives for the parent compound and metabolite M01 were obtained due to poor fit. Worst-case whole system half-lives of 4.3 days and 323 days were estimated for triazoxide and metabolite M01, respectively, based on results of the Lienden system.

The necessary surface water and sediment exposure assessments (Predicted environmental concentrations (PEC)) were carried out for triazoxide as well as the metabolites M01, M02 and M05 using the FOCUS step 1, step 2 and step 3 approach. For the metabolites M01 and M05 the available step 1 and step 2 values are relied on for the risk assessment. Detailed information about model parameterisation is provided in the list of end points in Appendix A.

The necessary groundwater exposure assessments were appropriately carried out using FOCUS scenarios and the models PEARL 3.3.3 and PELMO 3.3.2 for the active substance triazoxide and the metabolites M01 and M02. To assess the risk associated with preferential transport through structured soils the Chateaudun scenarios were also simulated using the MACRO model. Detailed information about model parameterisation is provided in the list of end points in Appendix A. The potential for groundwater exposure from the representative uses for these compounds above the parametric drinking water limit of 0.1 µg/L was concluded to be low in geoclimatic situations represented by all relevant FOCUS groundwater scenarios.

Triazoxide is not expected to significantly volatilize or to be subject to long-range transport in air.

The first-tier short-term TER values for granivorous birds were above the Annex VI trigger values, indicating a low risk. The margin of safety (TER=23.5) was considered to cover the uncertainty related to the derivation of a short-term toxicity end point, due to food avoidance (end point based on consumption in group where there was 30 % mortality). Further refinements were required to address the acute and long-term risk to birds. Based on yellowhammer as focal species, the acute TER value

was calculated to be 9.1. Yellowhammer would have to consume 159 (including a 10-fold uncertainty factor) seeds on an acute time scale to breach the Annex VI trigger. This number of seeds would cover approximately 3.45 m^2 of a field, and the number of seeds would cover 90 % of the daily food requirement of a yellowhammer. Furthermore, worst-case field studies indicated that yellowhammer could consume 1/3 of the critical number of seeds in one feeding event. Given these facts, in addition to the indication of food avoidance behaviour detected in the short-term dietary study, it was concluded that the risk to granivorous birds from consumption of treated seeds could be considered to be low on an acute timescale. The conclusion was supported by an additional assessment for a fast-feeding granivorous bird like the woodpigeon. A long-term risk assessment on reproductive birds was considered relevant for the spring use of triazoxide as a seed treatment. A refined long-term TER of 2.23 was calculated based on residue decline data for triazoxide in barley seed on soil surface. Further refinements were needed to address the long-term risk to granivorous birds from the spring use. Following the initial risk assessment, further data and refinements were considered during the resubmission. Four species were identified as focal species (skylark, chaffinch, woodpigeon and yellowhammer) in the Additional Report. Further information was provided supporting the proportion of the food obtained in the treated area (PT) for each focal species as well as the proportion of food types obtained from the treated crop (PD). The refined TER values were above the Annex VI trigger values for all representative focal species, therefore the long-term risk to granivorous birds for both the use in autumn and spring sown barley was assessed as low.

The tier 1 acute risk assessment for granivorous mammals was found to be low. Further refinements were required with regard to the long-term risk assessment for granivorous mammals. The refinements in the original review were based on wood mouse as focal species and on use of measured residue data, however they were considered as not satisfactory and further refinements were required to address the long-term risk to granivorous mammals. During the resubmission application further data were provided to refine the risk assessment. However, the higher tier risk assessment gave a TER_{lt} below the Annex VI trigger value, indicating a potential high long-term risk. Therefore, the long-term risk assessment to granivorous mammals needs further refinements and a data gap remains. The issue has been indicated as a critical area of concern.

Risk assessment of secondary poisoning and consumption of contaminated water was considered not relevant.

Triazoxide is proposed to be classified as very toxic to aquatic organisms. The acute and chronic risk to aquatic organisms was considered to be low. Furthermore, the risk to sediment-dwelling organisms from the metabolites M01, M02 and M05 was considered as low.

The acute risk to earthworms was considered to be low. The long-term risk from triazoxide and the soil metabolites M01 and M02 to earthworms was considered as low. Concerning other soil non-target macro-organisms, the risk to springtails was considered low for all potential soil residues. In addition, the potential risk from triazoxide and its metabolites to soil litter degradation processes was assessed as low.

The risk to bees and non-target arthropods was assessed to be low, as was the risk to soil non-target micro-organisms, biological methods of sewage treatment, and non-target plants.

KEY WORDS

Triazoxide, peer review, risk assessment, pesticide, fungicide

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BACKGROUND

Commission Regulation (EC) No 1490/2002[7], as amended by Commission Regulation (EC) No 1095/2007[8] lays down the detailed rules for the implementation of the third stage of the work programme referred to in Article 8(2) of Council Directive 91/414/EEC. This regulates for the European Food Safety Authority (EFSA) the procedure for organising, upon request of the Commission of the European Communities (hereafter referred to as 'the Commission'), a peer review of the initial evaluation, i.e. the Draft Assessment Report (DAR), provided by the designated rapporteur Member State. Triazoxide is one of the 84 substances of the third stage, part B of the review programme covered by the Regulation (EC) No 1490/2002, as amended by Commission Regulation (EC) No 1095/2007, designating the United Kingdom as rapporteur Member State.

In accordance with the provisions of Article 10(1) of the Regulation (EC) No 1490/2002, the United Kingdom submitted the report of its initial evaluation of the dossier on triazoxide, hereafter referred to as the DAR (The United Kingdom, 2007), received by EFSA on 25 June 2007. Following an administrative evaluation, the EFSA communicated to the rapporteur Member State some comments regarding the format and/or recommendations for editorial revisions, and the rapporteur Member State submitted a revised version of the DAR. In accordance with Article 11(2) of the Regulation (EC) No 1095/2007, the revised version of the DAR was distributed on 4 October 2007 to the sole applicant Bayer CropScience AG as identified by the rapporteur Member State, and on 5 November 2007 to the Member States for consultation.

The comments received on the Draft Assessment Report were evaluated and addressed by the rapporteur Member State. Based on this evaluation, EFSA identified and agreed on lacking information to be addressed by the notifier as well as issues for further detailed discussion at expert level.

Taking into account the requested information received from the notifier, a scientific discussion of the identified data requirements and/or issues took place in expert meetings in May – June 2008. 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 Member States in August 2008 leading to the conclusions set out in the EFSA Conclusion finalised on 30 September 2008 (EFSA, 2008).

Following the Commission Decision of 30 November 2009 (2009/860/EC)[9] concerning the non-inclusion of triazoxide in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing that substance, the applicant Bayer CropScience AG made a resubmission application for the inclusion of triazoxide in Annex I in accordance with the provisions laid down in Chapter III of Commission Regulation (EC) No. 33/2008[10]. The resubmission dossier included further data in response to the issues identified in the conclusions leading to the Decision on non-inclusion, as set out in the Review Report (European Commission, 2009a) as follows:

- the information available was insufficient to satisfy the requirements set out in Annex II and Annex III of Directive 91/414/EEC, in particular with regard to:
    - the available metabolism and residue data were not considered appropriate to conduct a robust consumer risk assessment due to the uncertainties identified with regard to the nature of residues in plant commodities and the possible transfer of residues in animal products
    - the long-term risk for granivorous birds

[7] OJ L224, 21.08.2002, p.25
[8] OJ L246, 21.9.2007, p.19
[9] OJ L 314, 1.12.2009, p.81
[10] OJ L 15, 18.01.2008, p.5

- the long-term risk for granivorous mammals
- the long-term risk to fish
- the long-term risk to earthworms

- and concerns were identified with regard to:

  - the consumer exposure

In accordance with Article 18 of Commission Regulation (EC) No. 33/2008, the United Kingdom, being the designated RMS in the resubmission procedure, submitted an evaluation of the additional data in the format of an Additional Report (The United Kingdom, 2010). The Additional Report was received by the EFSA on 10 June 2010.

In accordance with Article 19 of Commission Regulation (EC) No. 33/2008, the EFSA distributed the Additional Report to Member States and the applicant for comments on 16 June 2010. In addition, the EFSA conducted a public consultation on the Additional Report. The EFSA collated and forwarded all comments received to the Commission on 30 July 2010. The collated comments were also forwarded to the RMS for compilation in the format of a Reporting Table. The applicant was invited to respond to the comments in column 3 of the Reporting Table. The comments and the applicant's response were evaluated by the RMS in column 3.

In accordance with Article 20, following consideration of the Additional Report and the comments received, the Commission decided to further consult the EFSA. By written request, received by the EFSA on 30 August 2010, the Commission requested the EFSA to arrange a consultation with Member State experts as appropriate and deliver its conclusions on triazoxide within 6 months of the date of receipt of the request, subject to an extension of a maximum of 90 days where further information were required to be submitted by the applicant in accordance with Article 20(2).

The scope of the peer review and the necessity for additional information, not concerning new studies, to be submitted by the applicant in accordance with Article 20(2), was considered in a telephone conference between the EFSA, the RMS, and the Commission on 1 September 2010; the applicant was also invited to give its view on the need for additional information. On the basis of the comments received, the applicant's response to the comments, and the RMS' subsequent evaluation thereof, it was concluded that the EFSA should organise a consultation with Member State experts in the area of mammalian toxicology, and that no further information should be requested from the applicant.

The outcome of the telephone conference, together with EFSA's further consideration of the comments is reflected in the conclusions set out in column 4 of the Reporting Table. All points that were identified as unresolved at the end of the comment evaluation phase and which required further consideration were compiled by the EFSA in the format of an Evaluation Table.

The conclusions arising from the consideration by the EFSA, and as appropriate by the RMS, of the points identified in the Evaluation Table were reported in the final column of the Evaluation Table.

A final consultation on the conclusions arising from the peer review of the risk assessment took place with Member States via a written procedure in December 2010 – January 2011.

During the peer review of the DAR and the Additional Report and the consultation of technical experts no critical issues were identified for consultation of the Scientific Panel on Plant Protection Products and their Residues (PPR).

The conclusion from the original review was reached on the basis of the evaluation of the representative uses presented in the DAR, i.e. use as a fungicide as proposed by the notifier, which comprises seed treatment in barley against several agriculturally important diseases. The conclusions of the resubmission were reached on the basis of the evaluation of the same representative uses. A list

of the relevant end points for the active substance as well as the formulation is provided in Appendix A of this conclusion.

The documentation developed during the resubmission peer review was compiled as a Peer Review Report (EFSA, 2011), comprising of the documents summarising and addressing the comments received on the initial evaluation provided in the rapporteur Member State's Additional Report:

- the comments received;
- the resulting Reporting Table (rev. 1-1 of 2 September 2010)

as well as the documents summarising the follow-up of the issues identified as not finalised at the end of the commenting period:

- the Evaluation Table (1 February 2011);
- the report of the scientific consultation with Member State experts.

Given the importance of the Additional Report including its addendum (compiled version of January 2011 containing all individually submitted addenda) (The United Kingdom, 2011) 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. The documents of the Peer Review Report and the final addendum developed and prepared during the course of the initial review process are made publicly available as part of the background documentation to the original EFSA conclusion finalised on 30 September 2008 (EFSA, 2008).

THE ACTIVE SUBSTANCE AND THE FORMULATED PRODUCT

Triazoxide is the ISO common name for 7-chloro-3-imidazol-1-yl-1,2,4-benzotriazine 1-oxide (IUPAC).

Triazoxide belongs to the class of imidazole fungicides, alternatively classified as a benzotriazine fungicide. It is a contact and non-systemic fungicide; target organisms are killed on contact with the fungicide, although the mode of action is not known. Triazoxide is used in agriculture in seed treatment, only in mixture with other fungicides, to control a range of fungal diseases.

The representative formulated product for the evaluation was 'Raxil S FS 040', a flowable concentrate for seed treatment (FS), containing 20 g/L triazoxide and 20 g/L tebuconazole, registered under different trade names in Europe.

The representative uses evaluated comprise seed treatment against leaf stripe (*Pyrenophora graminea*), seed-borne net blotch (*Pyrenophora teres*) and smuts in winter and spring barley in northern Europe, at one treatment, with a maximum application rate of 6 g triazoxide/ha (3 g a.s./100 kg seed at the highest sowing rate of 200 kg seed/ha). Full details of the representative uses can be found in Appendix A to this report.

CONCLUSIONS OF THE EVALUATION

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

The following guidance documents were followed in the production of this conclusion SANCO/3030/99 rev.4 (European Commission, 2000), SANCO/10597/2003 – rev. 8.1 (European Commission, 2009b) and SANCO/825/00 rev. 7 (European Commission, 2004a).

The minimum purity of triazoxide technical material is 970 g/kg. There is no FAO specification available.

An additional source has been evaluated as part of the resubmission. A revised specification has been submitted, however this should be regarded as provisional as the following data gaps were identified:

- five batch data for the original source, analysed with a fully validated method of analysis, or alternatively, reanalysis of the old batches with the new method;
- quality control (QC) data to support the technical specification for the additional source. It should be noted that QC data are available, however in view of Commission Regulation (EC) No 33/2008 these could not be considered in the peer review.

Toluene was considered as a relevant impurity in the technical material with a maximum level of 3 g/kg.

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

Adequate analytical methods are available (HPLC-DAD) for the determination of triazoxide in the technical material and in the representative formulation, as well as for the determination of the respective impurities in the technical material.

Residues of triazoxide in food of plant and animal origin can be monitored by HPLC-MS/MS with a LOQ of 0.001 mg/kg (barley grain and straw, orange, tomato, rape seed and pea seed as well as milk, muscle, fat, liver, kidney and eggs). It should be noted however that methods for animal matrices are not needed as no residue definition for animal products was proposed. HPLC-MS/MS methods are available to monitor residues of triazoxide in soil with a LOQ of 0.001 mg/kg, and residues of

triazoxide in water with a LOQ of 0.1 µg/L. A data gap was identified for additional validation data for the monitoring method for the determination of the active substance in air, demonstrating that the LOQ is 0.3 µg/m³. Triazoxide residues in blood can be monitored by HPLC-MS/MS, with a LOQ of 0.05 mg/L.

2. Mammalian toxicity

The following guidance documents were used in the production of this conclusion: SANCO/221/2000 rev. 10 (European Commission, 2003), SANCO/22/200 rev. 7 (European Commission, 2004b) and SANCO/10597/2003 – rev. 8.1 (European Commission, 2009b).

Triazoxide was discussed by the experts in mammalian toxicology in June 2008 (PRAPeR meeting 49, round 10, subgroup 2) and in November 2010 (PRAPeR TC 44).

In the toxicological batches, most of the impurities were at lower amounts than in the proposed technical specification (April 2008). However, considering the assessment of the toxicological relevance of the impurities in the addendum to Volume 4 of the DAR (April 2008), the experts agreed that the proposed levels in the technical specification were not of toxicological concern. The same is applicable to the revised specification (The United Kingdom, 2010). Notwithstanding the level in the technical specification which does not raise any toxicological concern, the impurity 5 (toluene) should nevertheless be considered as relevant due to its potential for reproductive toxicity (Repro. Cat. 3; R63).

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

The absorption of triazoxide from the gastro-intestinal tract was rapid and almost complete. Its distribution within the body was widespread with the highest levels found in the liver and kidneys, without evidence of bioaccumulation. The major routes of excretion were via bile (64 – 75 %), urine (26 – 30 %) and faeces (< 10 %). Triazoxide was transformed into a large number of metabolites by deoxygenation, cleavages and conjugations. No single metabolite contributed to more than 6 % of the administered dose.

As the liver was not the primary target organ, the question was raised whether the amount excreted in bile was bioavailable. Even though the rapidity of the bile excretion (~43 % of the dose within 4 hours) would suggest a significant first pass metabolism, it was agreed that at least a part of the amount excreted in bile was available to the blood system (target organ) due to the entero-hepatic circulation, as well as widespread distribution of triazoxide in the body one hour after administration, and haemolytic effects appearing at very low doses. Therefore, the experts at PRAPeR 49 agreed on a bioavailability of 50 %, excluding the amount excreted in the bile during the first 4 hours after administration.

2.2. Acute toxicity

Different studies have been performed via the oral, dermal, inhalation, intravenous, intraperitoneal and subcutaneous exposure routes in a variety of species (rats, mice, cats and dogs). As a result, triazoxide was toxic after oral exposure or inhalation (rat oral LD_{50} 98 mg/kg bw, rat LC_{50} by inhalation 0.7 mg/L) with the proposed classification **T, R23/25 'Toxic by inhalation and if swallowed'**. Nevertheless, it was relatively non-toxic after acute dermal exposure (rat dermal LD_{50} > 5000 mg/kg bw) and did not cause skin irritation, eye irritation or skin sensitisation (Magnusson & Kligman's test).

2.3. Short-term toxicity

Short-term oral studies have been conducted in rats (28-day and 3-month studies) and dogs (3- and 12-month studies). Subacute inhalation and dermal studies have been performed with rats (21-day) and rabbits (21-day), respectively.

After oral administration in rats and dogs, the critical target was the blood system with the induction of compensated haemolytic anaemia, resulting in secondary effects in the spleen, liver, kidneys and bone marrow. Other effects were liver toxicity, increased white blood cells and proliferation of epithelial tissues (bile ducts, gall bladder and urinary bladder). The relevant short-term NOAEL for the rat was 0.21 mg/kg bw/day based on the 3-month rat study, and the relevant short-term NOAEL for the dog was 0.4 mg/kg bw/day based on the 1-year dog study. The adverse effects on the blood system observed in the rat studies would trigger classification with Xn, R48/22 'Harmful: danger of serious damage to health by prolonged exposure if swallowed'. However, in the dog study, haematological effects were found at a level (≤ 5 mg/kg bw/day), which would justify T, R48/25 'Toxic: danger of serious damage to health by prolonged exposure if swallowed'. Therefore, these classification proposals will have to be further considered by the EChA.

With regard to the subacute exposure by inhalation, the NOAEC in rats was 0.008 mg/L based on clinical signs, body weight effects, haematology and clinical chemistry changes, increased spleen weight and spleen congestion. Based on the severity of the haematological and splenic changes observed at a dose level lower than 0.075 mg/L, the experts at PRAPeR 49 agreed to propose the classification with **T, R48/23 'Toxic: danger of serious damage to health by prolonged exposure through inhalation'**.

Considering the subacute dermal exposure, the NOAEL in rabbits was 35 mg/kg bw/day based on a slight increase in liver enzyme activity (and dose adjusted for an exposure of 5 days per week).

2.4. Genotoxicity

A battery of five *in vitro* studies was presented in the DAR: the two Ames tests were negative, the gene mutation test with mammalian cells was negative, the UDS test with rat hepatocytes was negative, and the cytogenetic assay in human lymphocytes was positive in the absence of metabolic activation.

Among the four *in vivo* studies that have been performed, three were negative (cytogenetic assays in mice and hamsters and dominant lethal test in mice) and one was equivocally positive (the mouse micronucleus study), but this result was attributed to the haematotoxic effect of the test compound rather than genotoxicity. The overall weight of evidence indicated that triazoxide has no genotoxic potential *in vivo*.

2.5. Long-term toxicity

Long-term feeding studies have been performed in rats (2-year) and mice (21-month).

In the **rat** study, the adversity of the spleen effects at the lowest dose was extensively discussed by the experts at PRAPeR 49 and TC 44. Considering the dose-related increased incidence of darkly coloured spleen in females with a steep dose-response curve (even though there was no histopathological correlates) and the absence of mechanistic information, the experts decided to take a precautionary approach and to consider the lowest dose of 0.05 mg/kg bw/day (1 ppm) as a LOAEL.

In **mice**, the adverse effects were limited to a slight transitory change of bodyweight in males, and some equivocal histopathological changes without dose-response relationship, or were only evident in one sex (hyperplasia in the lung, lymphoid hyperplasia in the thymus and round cell infiltration in the sciatic nerve). Based on the increased incidence of lymphoid hyperplasia in the thymus of the males, the agreed NOAEL was 0.3 mg/kg bw/day.

In both species, the dose level for testing carcinogenicity could have been higher since the top dose levels produced only marginal effects. There were no treatment-related or significant increases in the incidences of tumours. Nevertheless, the experts agreed that the risk assessment could be performed with these studies, and that triazoxide did not show any carcinogenic potential up to the highest doses tested (25/100 ppm in rats and 25 ppm in mice).

2.6. Reproductive toxicity

In the rat multi-generation study, parental toxicity included increased spleen weight in males and increased ovarian weight in females, resulting in a parental NOAEL of 0.11 mg/kg bw/day. The reproductive NOAEL was the highest dose tested, i.e. 2 mg/kg bw/day, since no adverse effect on the reproductive parameters was observed. And finally, the NOAEL for the offspring was 0.11 mg/kg bw/day based on reduced pup survival during lactation in the second generation. Considering this effect on the pups in the second generation and the high residue value of triazoxide in fat shortly after administration, the experts at PRAPeR 49 agreed that triazoxide was likely to be found in milk and agreed to propose the classification **R64 'May cause harm to breastfed babies'**.

In the developmental studies, there were no signs of maternal toxicity in rabbits, or a reduced bodyweight gain in rats at the high dose level, resulting in a maternal NOAEL of 10 mg/kg bw/day for the rabbit and 3 mg/kg bw/day for the rat. It was noted that the critical effect on the red blood system had not been investigated in these studies. Considering the LOAEL of 5 mg/kg bw/day and the NOAEL of 1.5 mg/kg bw/day in the 28-day rat study, haematological and splenic effects might not be excluded in the rat developmental study at 3 mg/kg bw/day. Nevertheless, no developmental toxicity or teratogenic activity was observed in the species investigated up to the highest dose tested, resulting in a developmental NOAEL of 10 mg/kg bw/day for both rats and rabbits.

2.7. Neurotoxicity

Triazoxide is not a chemical with structural similarities to known agents producing a delayed neurotoxic response. Apart from the increased incidence of round cell infiltration in the sciatic nerve in the chronic mouse study (not considered relevant), there was no evidence of neurotoxicity in acute, short-term or long-term studies. Therefore no further testing is indicated.

2.8. Further studies

In the absence of any information on the metabolites, the experts at PRAPeR 49 meeting agreed that all metabolites should be considered comparable to the parent compound (which is toxic after single or repeated exposure).

2.9. Medical data

In the DAR, several reports on the medical status of employees working in plants manufacturing triazoxide were mentioned, and no poisoning incidents were known. Apart from skin reactions in some workers that were believed to be induced by the intermediate chlor-triazoxide, no detrimental health effects or long-term damage have been observed among employees.

2.10. Acceptable daily intake (ADI), acceptable operator exposure level (AOEL) and acute reference dose (ARfD)

Acceptable daily intake (**ADI**)

The ADI is **0.0002 mg/kg bw/day** (rounded from 0.00017 mg/kg bw/day), based on the LOAEL of 0.05 mg/kg bw/day in the 2-year rat study and using a safety factor of 300 (as proposed by the RMS in the Additional Report; The United Kingdom, 2010).

The additional safety factor of 3 was justified by the use of a LOAEL, the steep dose response in the rat chronic study and the absence of mechanistic information. It was also supported by the equivocally positive results in one *in vivo* genotoxicity study and the equivocal maternal NOAELs in the developmental studies.

Acceptable operator exposure level (**AOEL**)

The experts at PRAPeR 49 agreed to derive the AOEL from the 90-day rat study as proposed in the DAR, but with a correction for the bioavailability (50 %) in addition to the usual safety factor of 100. Therefore the resulting AOEL is **0.001 mg/kg bw/day**.

Acute reference dose (**ARfD**)

An ARfD was considered necessary for triazoxide based on the observed haematotoxic effects, especially in the micronucleus study where effects were seen after 2 doses. The proposed ARfD was **0.015 mg/kg bw,** based on the 4-week rat study and applying a safety factor of 100.

2.11. Dermal absorption

The potential dermal penetration of triazoxide from the formulation "**Raxil S FS 040**" and from the contaminated seed grains has been investigated *in vitro* (using rat and human skin) and *in vivo* (in rats). In the *in vitro* study the maximum flux values were used to derive a correction factor rat/human skin of 3.6 for the concentrate and 2.6 for the contaminated grain dust. Applying these correction factors to the values obtained in the *in vivo* study with rats gave dermal absorption values of **2.4 % for the concentrate** and 1 % for the contaminated grain dust. However, the experts at PRAPeR 49 agreed to double the value for the dust because of low recoveries in the *in vivo* study and inconsistent results *in vitro*, resulting in a dermal absorption value of **2 % for the contaminated grain dust**.

2.12. Exposure to operators, workers and bystanders

The representative plant protection product "Raxil S FS 040" is a seed dressing liquid formulation containing tebuconazole (20 g/L) and triazoxide (20 g/L), for use on barley seed at a maximum rate of 150 ml/100 kg seed. Estimates of exposure were provided for workers treating seeds (i.e. operators) and workers loading/sowing treated seed (i.e. workers).

Operator exposure during seed treatment

With the UK version of the Seed Tropex exposure model, even when applying different refinements (for cleaning and bagging), the estimated exposure was above the AOEL with the use of personal protective equipment (PPE: coverall and gloves) (see table below). Therefore the results of two field studies during use of "Raxil S FS 040" on barley seed were presented. Conducted under typical working conditions, they were considered as realistic and acceptable data to assess exposure to triazoxide. The resulting operator exposure was estimated to be up to 21 % of the AOEL with the use of coverall and gloves.

Worker exposure during seed loading/sowing

Based on Seed Tropex data, the exposure estimate during seed loading/sowing was above the AOEL with the use of coverall, even when applying a refinement for 6h exposure instead of 10h (see table below). A field study performed with a formulation containing prothioconazole was presented and considered acceptable to be extrapolated to triazoxide. In this study, the task of loading treated seed into a hopper of a drilling machine was regarded as contributing the most to exposure (compared to sowing of the treated seed). As a result, the exposure for workers sowing 15 ha of treated seed was estimated to represent 26 % of the AOEL, with the use of long-sleeved shirt and long trousers.

Estimated exposures in % of AOEL (0.001 mg/kg bw/day)

Model / Field study	Task of seed treatment*	Task of seed loading/sowing
Seed Tropex (UK version)	380	500°
Seed Tropex (refined)	123	300°
Field study	up to 21	26°°

* operators wearing coverall and gloves
° workers wearing standard protective garment i.e. coverall
°° workers wearing a single layer of clothing (long-sleeved shirt, long trousers)

Bystander exposure

It is not expected that levels of bystander exposure will exceed those of workers involved in loading/sowing treated seed (i.e. 26 % of the AOEL).

3. Residues

The conclusion in the residue section below is based on the guidance documents listed in the document 1607/VI/97 rev. 2 (European Commission, 1999) and the recommendations on livestock burden calculations stated in the 2004 and 2007 JMPR reports (JMPR, 2004, 2007).

Triazoxide was initially discussed in the PRAPeR 50 experts' meeting in June 2008 and an EFSA conclusion was issued in September 2008 (EFSA, 2008). For the resubmission, new plant and animal metabolism studies and additional residue trials were provided and evaluated in the Additional Report (The United Kingdom, 2010) in order to address the points that remained unresolved in the course of the first review.

3.1. Nature and magnitude of residues in plant

3.1.1. Primary crops

The metabolism study conducted on barley and initially evaluated in the DAR was considered not appropriate by the PRAPeR 50 meeting of experts to conclude on a residue definition for cereals, as no identification was performed in grain and straw, due to the low total radioactive residues observed at harvest (0.01 mg/kg and 0.04 mg/kg, respectively). Moreover, the experts expressed their concern regarding the possible presence in grains of triazoxide or of structurally related metabolites with similar toxicity properties, at very low levels, but of toxicological impact on the consumers, having regard to the extremely low ADI allocated to the parent compound. In addition, the absence of residues in grains at harvest could not be confirmed by the supervised residue trials, where analyses were performed using an inappropriate LOQ of 0.05 mg/kg. A data gap was therefore identified in the original review for a new metabolism study with further investigation in order to clarify the identity of residues in plant matrices and for further supervised residue trials.

A new metabolism study conducted on barley was therefore submitted in the framework of the resubmission procedure. Cereal grains were treated with ^{14}C-phenyl labelled triazoxide at dose rates of 3 g and 30 g a.s./100 kg seeds (1N and 10N). After sowing, the samples were taken after 42 days (forage) and at harvest after 180 days (grain and straw). Severe phytotoxic effects were observed in the 10N dose level, with the germination of the seeds being strongly reduced, and forage samples were not taken in the high dose plot in order to have sufficient plant material at maturity. For both doses, the TRRs were limited and similar in grain (0.0025 and 0.0035 mg/kg), and 0.0065 and 0.0130 mg/kg in straw in the 1N and 10N rate studies, respectively. Having regard to the low radioactive levels in grains, the identification of the metabolites was only conducted in the 1N forage and 10N straw samples. About 55 % of the radioactivity was extractable, of which 1 - 2 % was identified as parent triazoxide (0.0002 - 0.0004 mg/kg), 3 - 4 % as M02 (*c.a.* 0.0005 mg/kg), and 2 - 6 % as M01 (0.0003 - 0.0008 mg/kg), with the remaining extracted radioactivity being composed of 15 to 16 unknowns, each accounting for less than 9 % of the TRR. Since no individual compound was detected above

0.0009 mg/kg, even for the 10N dose rate, it can be concluded that neither the parent triazoxide nor any of its metabolites are expected to be present at detectable amounts when barley seeds are treated according to the representative GAP. Therefore, it is proposed to limit the residue definition for monitoring to the parent triazoxide only.

For risk assessment, having regard to the conclusion of the PRAPeR 49 meeting on mammalian toxicology concluding that all metabolites should be considered of comparable toxicity to the parent compound (see section 2.8), it is proposed to include in the residue definition, in addition to the parent triazoxide, the metabolites M01 and M02 identified in forage and straw. A conversion factor of 6 is proposed for risk assessment based on the respective proportions at which triazoxide, M02 and M01 were observed in straw (2.1 % / 4.0 % / 5.9 %).

The set of residue trials conducted on barley, oat, rye and wheat in northern Europe and initially evaluated in the DAR was considered not appropriate to propose a MRL for barley. No residues above the LOQ of 0.05 mg/kg were detected in grain and straw in any trials, but an exceedance of the ADI value initially proposed in the DAR (0.00005 mg/kg bw/day) could not be excluded when estimations were performed using the EFSA PRIMo model and the value of 0.05 mg/kg. A new residue data set, where samples are analysed with a more appropriate LOQ, was therefore required.

As requested, the applicant has submitted new residue trials where the samples were analysed for triazoxide using an analytical method achieving a LOQ of 0.001 mg/kg. The residues were below the LOQ in grain and straw in the six supervised residue trials conducted on barley in 2007, in northern and southern EU. Based on these data, the MRL was proposed at the level of LOQ (0.001 mg/kg). Such an unusually low value was proposed, having regard to the low ADI finally agreed during the PRAPeR TC 44 meeting on mammalian toxicology (0.0002 mg/kg bw/day), and considering the possible additional uses that could be envisaged on other cereals or other plant groups. The residue data are supported by the storage stability study showing triazoxide residues to be stable in cereal matrices (forage, straw and grain) up to 2 years when stored frozen at -18°C.

Data on the nature and magnitude of residues in processed products were not submitted and are considered not necessary as it was confirmed that residues in grains are not expected to be above 0.001 mg/kg.

3.1.2. Succeeding and rotational crops

Triazoxide may be considered to be highly to very highly persistent in soil (see section 4.1). The uptake and distribution of triazoxide residues in rotational crops were investigated in clover and turnips. The crops were grown in soil that had previously been used to grow barley, which had been treated with a seed treatment application of phenyl ring labelled [^{14}C] triazoxide, at a rate of 19 g a.s./ha (approx. 3N). The crops were planted 131 days after planting the treated barley seed, once the primary crop had been harvested. At harvest the TRR in the mature clover and turnip leaves and roots was less than 0.001 mg/kg. In view of the very low total residues in the plant samples, an investigation of the metabolism in the plants was not undertaken. An imidazole ring labelled triazoxide study for rotational crops was not submitted because residues were very low in the phenyl ring labelled rotational crop study.

It was noted by the PRAPeR 50 meeting of experts that only clover and turnip were planted as succeeding crops and that only one plant back interval of 131 days was studied. However, the experts considered that the necessary 3 crop categories were covered: clover (leafy crops) and turnip (root/ tuber crops) were investigated in the study, and in addition, cereals (seed treated barley) could be taken into account as pre-emergence treated crop. According to the current guidance documents field tests with rotated crops should be conducted at a 30-day, 120-day and 365-day plant-back interval. It was however noted that because of the degradation rates of triazoxide and its metabolites in soil (DT_{50}/ $DT_{90;}$ see section 4.1), it does not seem necessary to require further rotational crop data at plant-back intervals shorter than the one studied, since the residue levels in soil were likely to decrease only very slowly, and hence insignificantly over 130 days. The available rotational crop data with 131-day plant-

back interval are therefore deemed to adequately reflect the levels of residues expected at any of the test intervals proposed in the guidance documents.

The experts noted that, considering the higher application rate at which the rotational crop study was performed when compared to the representative use, and the fact that the total radioactive residues in mature following crops (clover, turnip) were below 0.001 mg/kg, no concern is expected with regard to consumer exposure from rotated crops for human consumption, despite the low ADI of triazoxide.

3.2. Nature and magnitude of residues in livestock

No animal metabolism studies were submitted and evaluated in the DAR, the estimated intakes being below the trigger value of 0.1 mg/kg DM as set out in the guidance documents. However, concerns were raised regarding the possible presence of residues in ruminant matrices, even at very low levels, given the very low ADI proposed for this active substance.

Consequently, the applicant provided a goat metabolism study in the framework of the resubmission, where animals were dosed over five consecutive days with ^{14}C-phenyl-labelled triazoxide at a rate of 4.3 mg/kg DM. This dose level is estimated to represent a 1000 N and 600 N dose level for dairy and beef cattle respectively, when animal intakes are calculated using a residue level of 0.006 mg/kg in cereal grain and straw (0.001 mg/kg x CF 6). The total radioactive residues were < 0.01 mg/kg in muscle and fat, 0.02 mg/kg in milk, 0.13 mg/kg in kidney, and 0.26 mg/kg in liver. The identification of the residues was not investigated in any animal tissues, but considering the exaggerated dose rate at which the study was conducted, it can be concluded that total residues, and therefore individual compounds, are not expected to be above 0.0005 mg/kg in any goat matrices. The setting of a residue definition and proposing MRLs in animal products were therefore not considered necessary.

3.3. Consumer risk assessment

The chronic and acute consumer risk assessment was conducted using the EFSA PRIMo model, the MRL value of 0.001 mg/kg proposed for barley, and the conversion factor of 6 for risk assessment. No concern was identified, with the TMDI being less than 4 % of the ADI (0.0002 mg/kg bw/day) for all the diets included in the EFSA model and the IESTI less than 0.1 % of the ARfD (0.015 mg/kg bw).

Concerns were raised in the course of the first review on the possible presence of triazoxide and its metabolites M01 and M02 in groundwater, given the low ADI, although the predicted levels were calculated to be below 0.1 µg/L. New estimates carried out according to the WHO Guideline (WHO, 2009) and using the predicted levels of triazoxide, M01 and M02 in groundwater (< 0.0001 µg/L) show the contribution of the residues in drinking water to be insignificant (< 0.1 % ADI).

3.4. Proposed MRLs

Based on the new residue data set submitted by the applicant in the framework of the resubmission, a MRL for barley grain is proposed at the LOQ of 0.001* mg/kg.

The setting of residue definitions and proposing MRLs for products of animal origin were considered not necessary, given the results of the goat metabolism study evaluated in the Additional Report (The United Kingdom, 2010).

4. Environmental fate and behaviour

The fate and behaviour of triazoxide in the environment was discussed in the PRAPeR 47 meeting of experts (May 2008). All fate and behaviour studies were performed with triazoxide [^{14}C] radiolabelled at the phenyl ring. The justification for not performing studies with the substance labelled at the imidazol ring presented in the dossier was found acceptable. Within the resubmission procedure an Additional Report bringing the assessment up to current guidelines was submitted in June 2010 (The United Kingdom, 2010).

4.1. Fate and behaviour in soil

4.1.1. Route of degradation in soil

The route of degradation of triazoxide in soil under dark aerobic conditions at 20°C was investigated in four soils (pH 5.9 – 7.6; OC 0.4 – 2.1 %; clay 2.3 – 12.0 %) maintained at 40 – 50 % MWHC. The degradation proceeds initially either through reduction to produce M01 (max. 12.8 % AR at 30 DAT), or through loss of the imidazole moiety to produce M02 (max. 9.0 % AR at 3 DAT[11]). Unextracted residues amounted up to a maximum of 29.8 % AR after 120 days (end of the study). Mineralization was practically negligible in the four soils tested (max. CO_2 = 0.1 % AR).

The degradation of triazoxide was also investigated under dark anaerobic conditions at 20°C in one soil (pH 7.6; OC 2.1 %; clay 10.2 %). Metabolite M01 reached the maximum of 25.5 % AR at the end of the study, 155 DAT (125 d after flooding). Up to three non-identified metabolites were found in the anaerobic study. These metabolites did not exceed individually 4.9 % AR. Unextracted radioactivity reached a max. 28.1 % AR at the end of the study.

Photolysis was investigated in one soil (pH 7.6; OC 2.1 %; clay 10.2 %). Photolysis slightly enhances the degradation of triazoxide, but it is not expected to contribute significantly to its environmental dissipation.

4.1.2. Persistence of the active substance and their metabolites, degradation or reaction products

The rate of degradation in soil was investigated in the same studies presented in the route section (4.1.1). Triazoxide may be considered to exhibit high to very high persistence in soil under dark aerobic conditions at 20 °C ($DT_{50\ lab\ (biphasic\ kinetic,\ overall)}$ = 208 – 278 days). The rate of degradation of the metabolite M01 was calculated by the applicant with the data of the experiments performed with the parent compound by SFO based kinetic analysis, assuming a formation fraction of 1 ($DT_{50\ lab}$ = 4.7 – 29.9 days). However, at least for one of the soils no apparent decline of the metabolite concentration is observed after the maximum, and therefore the reliability of the values obtained are not completely satisfactory. The RMS recalculated the dissipation half-lives by non-linear regression of the data after the maximum concentration of metabolite is reached. In this calculation M01 was moderately persistent in soil (decline $DT_{50\ lab}$ = 32.4 – *347* days). The longest value (*in italics*) corresponds to the situation where no decline is observed, and was considered as not reliable; therefore, the next worst-case half-life (DT_{50} = 56.7 days) was considered to represent a realistic worst-case degradation of M01 in soil. These values were agreed by the meeting of experts as input parameters for environmental exposure calculations in soil, together with a maximum relative M01 amount of 17.7 % (on molar basis, from maximum observed in field studies) of the parent applied.

Field dissipation studies were performed in four sites, two in the northern EU (Germany, UK; pH 7.4 – 8.4; OC 0.9 – 1.3 %) and two in southern EU (South France, Italy; pH 8.2 – 8.7; OC 1.2 – 1.3 %). In this second study the metabolites M01 and M02 were measured in soil. Following the recommendation of FOCUS kinetics (FOCUS, 2006) a kinetic analysis of the field dissipation data to derive degradation rates and formation fractions of the parent compound and the metabolites was provided using a Q10 of 2.58 (EFSA, 2007) and Walker equation coefficient of 0.7 within the resubmission application.

Under field conditions the persistence of triazoxide was high ($DT_{50,\ field\ (biphasic\ kinetic,\ overall)}$ = 18 – 99 days, DT_{90} = 640 – 1080 days), that of M02 high (decline M02 $DissT_{50\ field}$ = 239 – 313 days; excluding the UK field trial where no decline is observed), while the degradation rate for M01 could not be assessed from the available field data (no decline was observed).

[11] In field dissipation studies metabolite M02 accounted for up to 18.7 % (molar basis) of the triazoxide applied after 14 and 140 days.

Predicted environmental concentrations (PEC) in soil were calculated for triazoxide and its major soil metabolites following standard procedures. Since the worst-case field DT_{90} of triazoxide is above 365 days the RMS also calculated accumulation of triazoxide in soil and the maximum amounts of M01 that may be expected to be formed from the maximum accumulated parent. As M02 has DT_{90} > 1 year accumulated PEC were calculated for this metabolite, using a DT_{50} of 313 days.

4.1.3. Mobility in soil of the active substance and their metabolites, degradation or reaction products

Two batch equilibrium adsorption/desorption studies in a total of four soils (pH 5.4 – 6.7; OC 0.9 – 2.4 %; clay 2.3 – 10.2 %) were performed with triazoxide. Triazoxide may be considered low to medium mobile in soil (K_{foc} = 245 – 1743 mL / g). A batch equilibrium adsorption/desorption study with three soils (pH 6.3 – 6.7; OC 0.8 – 2.1 %; clay 5.0 – 12.0 %) was performed with metabolite M01. M01 may be considered slightly mobile under these conditions (K_{foc} = 2053 – 4148 mL/g). Finally, a batch equilibrium adsorption/desorption study with three soils (pH 6.0 – 6.4; OC 1.1– 2.6 %; clay 8.9 – 14.7 %) was performed with metabolite M02. M02 may be considered low to medium mobile under these conditions (K_{foc} = 385.6 – 1709.0 mL/g). The RMS noted the narrow range of pH and the ionisable character of metabolite M02. Whereas a large margin of safety is considered to exist for the representative use, further data could be needed if other uses at significantly higher application rates are applied for in the future.

4.2. Fate and behaviour in water

4.2.1. Surface water and sediment

The hydrolysis of triazoxide in buffered aqueous solutions (pH 4, 7, 9) was investigated in a study at 50°C. In this study triazoxide was stable at pH 4. An additional study was performed at 25°C to investigate hydrolysis at pH 7 and 9. Under these conditions triazoxide was practically stable at pH 7 and readily hydrolyses at pH 9 (DT_{50} = 6.6 days). The main hydrolysis metabolite was M04 (max. 97.3 % after 30 days).

Aqueous photolysis of triazoxide under artificial simulated sunlight (Xe lamp filtered for λ < 290 nm) was investigated in one study in sterile buffered aqueous solution (pH 7) at 25 °C. Triazoxide is rapidly photolysed in water (DT_{50} = 24.4 h equivalent to 3.5 natural solar days at 33 ºN) to yield the major metabolite M05 (max = 49.2 % after 60 h), and ten additional minor metabolites. An additional study is available for the determination of photolysis and quantum yield of triazoxide and its metabolite M05. According to this study, the photolysis half-life of triazoxide in water is expected to range from 1.7 to 9.7 days, depending on the season and the latitude (30 – 50 ºN).

No ready biodegradability study is available and therefore triazoxide is considered not readily biodegradable.

The dissipation and degradation of triazoxide in aquatic systems was investigated in a laboratory study with two different water / sediment systems (pH_{water}: 7.7 – 8.9; OC_{sed} = 0.9 – 4.1 %; $clay_{sed}$: 9.2 – 14.9 %) at 22°C. The ratio of sediment to water exceeded the SETAC recommendations (Lynch MR., 1995) (1:3 in the study with respect to the recommended range 1:4 – 1:10). Therefore, the adsorption to the sediment may have been overestimated in this study. Triazoxide dissipated rapidly from water to sediment phase and broke down to form the metabolites M01 (max. 47.4 % AR in the sediment after 30 days based on TLC analysis) and M05 (max. 9.8 % AR in the sediment after 60 days based on TLC analysis, higher amounts were determined when HPLC was used for quantification). Unextractable residues in the sediment amounted up to 55.7 % AR in the sediment after 91 days. Mineralization was negligible in both systems (max. CO_2 < 1 % AR after 91 days). The limited sampling regime of these experiments (no samples were taken from day 0 to 15) prevents the calculation of reliable kinetic parameters. However, a simple non-linear kinetic analysis was presented by the applicant to derive dissipation and degradation rates of triazoxide and M01 in the water sediment systems. This kinetic analysis was only partially validated (only whole system results for the Lienden system were

confirmed). For the IJzendoorn system, no reliable whole system half-lives for the parent and metabolite M01 were obtained due to poor fit. Worst-case whole system half-lives of 4.3 days and 323 days were estimated for triazoxide and M01, respectively, based on results of the Lienden system. PEC surface water and sediment calculations were based on FOCUS (FOCUS, 2001) step 1, step 2 and step 3[12] for triazoxide and the metabolite M02. For the metabolites M01 and M05 the available step 1 and step 2 values are reliable and are appropriate for use in the risk assessment[13]. Detailed information about model parameterisation is provided in the list of end points in Appendix A.

With regard to the exposure of surface waters, a Member State commented during the peer review of the resubmission application that it was possible that when seed was drilled and the quality of the seed treatment was not optimal, abrasion could result in the formation of dust. If formed, it cannot be excluded that this dust could drift to reach adjacent surface water at the time of sowing. This exposure route to surface water has not been addressed in this EU level exposure assessment. Consequently, the risks associated with this exposure route have not been characterised.

4.2.2. Potential for ground water contamination of the active substance and their metabolites, degradation or reaction products

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (FOCUS, 2000) scenarios and models (PEARL 3.3.3 and PELMO 3.3.2)[14] for the active substance triazoxide and the metabolites M01 and M02. To assess the risk associated with preferential transport through structured soils the Châteaudun scenarios were also simulated using the MACRO model. Detailed information about model parameterisation is provided in the list of end points in Appendix A. The potential for groundwater exposure from the representative uses for these compounds above the parametric drinking water limit of 0.1 µg/L was concluded to be low in geoclimatic situations represented by all relevant FOCUS groundwater scenarios.

4.3. Fate and behaviour in air

Triazoxide is not expected to significantly volatilize based on its physical and chemical properties (Henry Law constant = 7 x 10^{-7} Pa x m^3 /mol). A half-life in the troposphere of 10.5 h was calculated assuming 0.5 x10^6 radicals/cm^3 (global 24 h mean). Therefore, triazoxide is not expected to be subject to long-range transport via air.

5. Ecotoxicology

The risk assessment was based on the following guidance documents: European Commission (2002a, 2002b, 2002c) and SETAC (2001).

Triazoxide was discussed in the PRAPeR 48 meeting of ecotoxicology experts in May 2008, on the basis of the DAR (The United Kingdom, 2007). Within the resubmission procedure an Additional Report was submitted in June 2010 (The United Kingdom, 2010).

5.1. Risk to terrestrial vertebrates

The acute toxicity study indicated that triazoxide was of moderate oral toxicity to birds and that mortality was usually preceded by severe diarrhoea. In the two short-term dietary studies the conversion of the dietary concentration into a daily dietary dose presented some problems due to the strong food avoidance reported below the LC_{50} level. In fact, the short-term toxicity studies appeared to be mediated through reduced food consumption. It was therefore proposed to use surrogate LD_{50}

[12] Simulations correctly utilised the agreed Q10 of 2.58 (EFSA, 2007) and Walker equation coefficient of 0.7. As the product is not sprayed, the parameterisation also followed the EFSA (2004a) Opinion.

[13] Whilst the applicant's resubmission dossier also contained step 3 calculations for metabolites M01 and M05, the information reported on how the formation of the metabolites was implemented in the modelling was insufficient for these results to be relied on. However, this has no consequence as the risk assessment for these two metabolites could be concluded using step 1 and if necessary step 2 values (see section 5.2).

[14] Simulations correctly utilised the agreed Q10 of 2.58 (EFSA, 2007), Walker equation coefficient of 0.7 and were in accordance with the EFSA (2004b) Opinion.

values of approximately 268.1 mg a.s./kg bw/day for the mallard duck (*Anas platyrhyncus*) (calculated from the dose which resulted in 30 % mortality). A reproductive NOEC of 11.7 mg a.s./kg bw/day was identified, based on the available reproduction study with Japanese quail (*Coturnix japonica*). The tier I assessment provided TER values above the Annex VI trigger for the short-term risk to granivorous birds. The TER value of 23.5 was more than twice the level of the Annex VI trigger, and it was considered that the margin of safety would cover the uncertainty related to the derivation of the short-term toxicity end point.

Further refinements were required to address the acute (TER = 7.9) and long-term risk (TER = 1) to granivorous birds. Yellowhammer (*Emberiza citrinella*) was considered as more appropriate focal granivorous species to be found on fields with an estimated surface density of 46 seeds/m^2 (equal to 10 % of sowing density), than the linnet (*Carduelis cannabina*), which would require higher surface density of seeds. The TER value for yellowhammer was calculated to be 9.1. It was estimated that a yellowhammer could consume 159 seeds per day to achieve the median LD_{50}, including an assessment factor of 10, based on the acute toxicity of triazoxide and seeds containing 1.5 µg triazoxide/seed. It was evident from field studies (Prosser, revised March 2001), that yellowhammer may consume up to 1/3 of the 159 seeds in a single feeding event. It was considered that the field study may have been a worst case due to the high availability of spilled seeds. Furthermore, it was estimated that if the yellowhammer should consume 159 seeds, it would have to take all seeds over an area of 3.45 m^2, and this consumption would cover approximately 90 % of the daily food intake. The revised risk assessment for the yellowhammer assumed that all of the treated seed was consumed over an acute timescale. The dietary studies indicated, however, that triazoxide treated seed was potentially unpalatable, with birds appearing to starve themselves rather than eating it. In these studies, when consumed over the course of a day, test birds were able to withstand a higher intake of triazoxide compared to the acute study. This indicated that birds could potentially metabolise and excrete the active substance, and hence have an improved chance of survival following what could otherwise have been a lethal dose.

It was suggested that spillages could be risk managed using appropriate labelling/user awareness campaigns. As a consequence, birds would have to forage more in order to locate treated seeds, which in effect would increase the time over which consumption occurred, and increase the potential for metabolism and excretion of any ingested triazoxide. For relevant small granivorous species the number of treated seeds required to be consumed over an acute timescale was considered likely to be more than would be realistically achieved. In addition, those species which are known to feed more rapidly than the potential mitigation which might be afforded by metabolism and excretion, may prove to be less effective in reducing exposure. The Prosser field work indicated that some fast-feeding medium-sized birds were also attracted to the bait stations. The fast-feeding woodpigeon (*Columba palumbus*) was found to consume up to 590 barley seeds in a single feeding event. Furthermore, it was assumed that a medium sized bird, such as a woodpigeon, could consume 10 % of its bodyweight/day, which was equivalent to approximately 1000 seeds. Based on the acute toxicity including an assessment factor of 10, it was estimated that the woodpigeon may consume 2940 contaminated barley seeds without any risk. The latter assessment for woodpigeon supported the conclusion that the risk from consumption of treated barley seed on an acute timescale was considered to be low for granivorous birds.

In the refined long-term risk assessment for granivorous birds it was considered that the autumn/winter use of triazoxide as seed dressing in the northern Member States would be outside the breeding season. The potential risk could be considered as low, whereas this was not the case for the use in spring. The long-term risk assessment was therefore revised by use of measured residue decline data in barley seeds on soil surfaces to refine the 10 days f_{twa}. The TER value of 2.23 calculated on basis of a refined f_{twa} of 0.46 and a standard granivorous bird indicated further need for refinement. The use of yellowhammer and woodpigeon as focal species was proposed. Whereas a TER value of 7.1 indicated a low risk to woodpigeons, the risk was still found to be high for yellowhammer (TER = 2.6). Following on from the initial assessment, additional data were submitted in the resubmission and were used to refine the risk assessment. Four species were identified as focal species (skylark, chaffinch,

woodpigeon and yellowhammer) based on studies provided in the Additional Report. Further information was provided supporting the proportion of the food obtained in the treated area (PT) for each focal species as well as the proportion of food types obtained from the treated crop (PD). The refined TER values (see Appendix A) were above the Annex VI trigger values for all representative focal species, therefore the long-term risk to granivorous birds for both the use in autumn and spring sown barley was assessed as low.

In addition to the acute and long-term mammalian toxicological end points for triazoxide, a feeding study on house mice (*Mus musculus*) was provided by the applicant to support a repellency factor. It was however concluded that no significant repellency factor could be derived from the study. The tier 1 risk assessment for granivorous mammals gave an acute TER value of 14.2, i.e. above the Annex VI trigger and indicating a low risk. For the long-term risk assessment the TER value was below the trigger (TER = 0.3). It was considered that the use of triazoxide on autumn/winter sown barley was unlikely to pose a significant threat to mammal populations in many northern Member States, as this would be outside the reproductive season. If mammals reproduce during autumn/winter in certain Member States, then further information to refine the long-term risk would be required. The representative use on spring sown barley however required further consideration. Wood mouse (*Apodemus sylvaticus*) was used as focal species and a 10-d f_{twa} was applied to the initial nominal seed loading based on residue decline data, in line with the refinements for birds. The refinement of avoidance, de-husking, PD- and PT-factors proposed by the applicant was however not considered satisfactory, and required further supportive data. Following the initial assessment additional ecological data were submitted in the resubmission that indicated that the PD value could be set up to 0.66. Data on PT were submitted, however, due to the uncertainties regarding the number of individuals tracked and the population surveyed, they were not used in the risk assessment. Data on de-husking as well as palatability of the treated seed were not considered to be appropriate to quantitatively refine the risk assessment. The higher tier risk assessment gave a TER_{lt} of 0.97, below the Annex VI trigger value, indicating a potential high long-term risk for granivorous mammals. Therefore, the long-term risk assessment for granivorous mammals needs further refinements and the data gap remains.

The risk to earthworm- and fish-eating birds and mammals from secondary poisoning was not assessed as the $logP_{ow}$ of triazoxide was less than 3.

The two major soil metabolites M01 and M02 were predicted to be present in soil at lower levels than the parent triazoxide (see Appendix A). Metabolite M01 has a $logP_{ow}$ of <3.0 and was therefore not expected to bio-accumulate. The $logP_{ow}$ for the metabolite M02 was not known precisely, but was considered unlikely to be much greater than 3.0. A theoretical assessment of the risk to earthworm- and fish-eating birds, assuming comparable toxicity to the parent triazoxide and a worst-case $logP_{ow}$ of 6, indicated a low risk.

The method of application (as treated seed incorporated into soil) is expected to preclude significant contamination of puddles of water on the soil surface. Hence, exposure of birds and mammals via drinking contaminated water was not assessed.

5.2. Risk to aquatic organisms

Based on the available acute toxicity data, triazoxide is proposed to be classified as very toxic to aquatic organisms. The lowest end point value for technical triazoxide driving the aquatic risk assessment was obtained for algae, with an E_bC_{50} of 0.039 mg a.s./L. No studies were presented to demonstrate the toxicity of the formulation "Raxil S FS 040" to aquatic life, as "Raxil S FS 040" is used for seed treatment, and from the representative use it would not be expected to contaminate surface waters directly. Moreover, the formulation composition was not expected to be sufficiently conserved in soil to contaminate surface water via other routes. Consequently, no assessment of the risk to aquatic life from the formulation was required. With regard to the exposure of surface waters, during the resubmission it has been noted that the exposure route to surface water from possible dust formation during sowing has not been addressed in the EU level exposure assessment (see section

4.2.1). Therefore, the environmental risks associated with this exposure route have not been investigated.

Based on FOCUS step 2 PECsw estimations, all the acute TERs were above the Annex VI triggers, indicating a low risk from the parent triazoxide. TER calculations were not provided for FOCUS step 3 as PECsw was clearly lower than PECsw from FOCUS step 2 (see Appendix A).

A chronic risk assessment for aquatic organisms was not provided in the DAR, as no chronic studies were available. The chronic risk assessment was discussed in the PRAPeR 48 meeting of experts during the original review. Since there was only a small margin of safety from the acute test (fish TER = 154), and no information about long-term exposure was available, the experts were of the opinion that an additional chronic study was needed for fish to address potential chronic risk[15]. However, during the resubmission procedure it was considered that a chronic toxicity study is no longer necessary due to the very low exposure identified at FOCUS sw step 3, based on which the chronic risk to aquatic organisms from the representative uses of triazoxide as a seed treatment was considered as low.

The risk to aquatic organisms from the metabolites M01, M05 and M02 was assessed based on surrogate data of 10 times higher toxicity than the parent triazoxide toxicity and up to FOCUS step 2 PECsw calculations. The TER values were above the Annex VI trigger and the risk to aquatic organisms from these metabolites was considered to be low.

In sediment, metabolites M01, M02 and M05 reached levels that triggered exposure assessment. For metabolite M01 a low risk to sediment-dwelling organisms was indicated based on a sediment-spiked Chironomid study and FOCUS step 1 PEC sediment. Metabolite M05 represents a further degradation step of M01, and was predicted to occur at lower concentrations than M01, therefore the risk to sediment-dwelling organisms from M05 was considered to be covered by the assessment for M01. Additionally, the risk from the metabolite M02 was considered to be addressed by the risk assessment for M01, based on the facts that M02 represents a degradation step from M01 and the predicted sediment concentration was similar to the estimated concentration of M01 (see Appendix A).

Bio-accumulation was not considered an issue, as the $\log P_{ow}$ is less than 3.

5.3. Risk to bees

The oral and contact toxicity of technical triazoxide to bees was low, based on the available data. For the representative use as a seed treatment the hazard quotient (HQ) approach is not considered appropriate. Given that the only representative use is as a seed treatment, and considering that triazoxide is not a systemic substance the risk to bees is considered to be low. No further data or refinements are considered necessary.

5.4. Risk to other arthropod species

The dose for the representative use of triazoxide as a seed treatment was estimated to be equivalent to 6 g a.s./ha. Glass plate studies with the two indicator species, *Aphidius rhopalosiphi* and *Typhlodromus pyri* were conducted with an experimental formulation containing triazoxide at concentrations comparable to the representative GAP. No effects on mortality or reproductive capacity were reported at this level of exposure. These contact studies were, however, considered to be of less relevance to triazoxide, because it is used as a seed treatment and furthermore, because it was considered to be of limited systemicity. The applicant provided extended laboratory studies with the rove beetle (*Aleochara bilineata*), the carabid beetle (*Poecilus cupreus*) and the wolf spider (*Pardosa spp*). These additional species were exposed to seeds treated with the representative formulation

[15] During the initial peer review triazoxide was regarded as belonging to the group of imidazoles, which are considered to be potential endocrine disrupters. Member State experts considered that the potential for endocrine disruption should be addressed. After the initial peer review, however, due to the chemical structure and mode of action, it was concluded that there were no reasons to suspect endocrine disrupting properties of triazoxide.

("Raxil S FS 040") in the range of the expected rate of use. Effects on relevant end points (i.e. mortality, feeding capacity or reproduction) did not exceed the Annex VI trigger limit of 50 %.

Overall, it was concluded that the risk to non-target arthropods when the formulation "Raxil S FS 040" was used as a seed treatment would be low for the representative uses.

5.5. Risk to earthworms

Laboratory studies indicated that the parent triazoxide, its two main soil metabolites M01 and M02, and "Raxil S FS 040" were of low acute toxicity to earthworms. Based on peak plateau soil concentration the TER values for technical triazoxide, "Raxil S FS 040", metabolites M01 and M02 were all several orders of magnitudes above the Annex VI trigger, indicating a low acute risk to earthworms for the representative use of triazoxide. A long-term risk assessment was required for triazoxide as the worst-case field DT_{90} was 1080 days. The long-term study using "Raxil S FS 040" treated seed did not fully address the potential toxicity of residues in the soil matrix. New data on the chronic toxicity of the formulation 'Triazoxide FS 050' (solo formulation) to earthworms were evaluated in the Additional Report, and the chronic risk to earthworms from triazoxide was assessed as low. A new chronic toxicity study of the metabolite M01 was also evaluated in the Additional Report. Based on the end point set out in this study the chronic risk of metabolite M01 to earthworms was assessed as low. For the metabolite M02 no study on chronic toxicity to earthworms was submitted, however, a weight of evidence approach was presented. The maximum PECsoil including accumulation for this metabolite was calculated to be 2.14 µg/kg soil. This means that a NOEC of 10.7 µg/kg dry weight soil for the metabolite M02 would be sufficient to reach a TER of 5. This value can be compared with the results gained in the studies on earthworms and other soil organisms with the metabolite M01. A chronic study with earthworms (*Eisenia fetida)* resulted in a NOEC of 10 mg/kg dry weight soil for the metabolite M01. Compared to a theoretical NOEC of 10.7 µg/kg dry weight soil for metabolite M02, this means that even if the metabolite M02 was more than 900-fold more toxic than the metabolite M01, the TER of 5 for the metabolite M02 would still be passed. The chronic study with the metabolite M01 and the soil arthropod *Folsomia candida* resulted in a NOEC of 100 mg/kg dry weight soil. Compared to a theoretical NOEC of 10.7 µg/kg dry weight soil for metabolite M02, this means that even if the metabolite M02 was more than 9300-fold more toxic than the metabolite M01, the TER of 5 for the metabolite M02 would still be passed. Compared to the active substance, the metabolite M01 has lost one functional group while metabolite M02 has lost two functional groups.

The above argument was considered reasonable and therefore no additional data are required to conclude on a low chronic risk of metabolite M02 to earthworms.

Overall, it was concluded that both the acute and chronic risk to earthworms was low from the representative uses of triazoxide.

5.6. Risk to other soil non-target macro-organisms

Triazoxide is highly to very highly persistent in soil; metabolite M01 is moderately persistent while metabolite M02 exhibits high persistency in soil (see sections 4.1.2 and 7.1). For triazoxide, soil metabolite M01, and the representative formulation "Raxil S FS 040" a low risk to the springtail (*Folsomia candida*) was identified, using laboratory reproduction studies and PEC peak plateau values. The TERs for triazoxide, metabolite M01 and "Raxil S FS 040" were orders of magnitude above the Annex VI trigger, indicating a low risk. For soil metabolite M02, a structural-similarity argument, that the risk to this group of organisms will not be greater than in case of metabolite M01, was considered sufficient (see also section 5.5). A soil functionality test (litter bag study) conducted using "Raxil S FS 040" treated seed was submitted during the original review. The relevance of this study could not be established as it was unclear whether the litter bags had been sufficiently exposed to triazoxide. A new litter bag study was carried out to address the concerns highlighted with the original study. The study indicated that there was > 60 % of leaf litter degradation compared to the control in soil treated with 0.009 mg a.s./kg soil. The exposure was in line with the predicted

concentration, therefore the risk was assessed to be low. As regards the risk from metabolites M01 and M02, the risk was considered addressed in the new litter bag study.

Overall, it was concluded that the risk to springtails was low for all potential soil residues, and the potential risk to soil litter processes from triazoxide and the soil metabolites M01 and M02 was also considered addressed.

5.7. Risk to soil non-target micro-organisms

Compared to the control, technical triazoxide and metabolite M01 had no effects > 25 % after 28 days on nitrogen transformation at a soil concentration of 0.038 and 0.036 mg/kg soil, respectively (exceeding the PEC plateau concentration expected from the representative use of triazoxide). The formulation "Raxil S FS 040" had no effects > 25 % on soil respiration and nitrogen transformation after 28 days at a dose rate 4.8 times higher than the maximum representative rate. No specific studies were presented to demonstrate the effect of the metabolite M02 on respiration and nitrogen transformation. However, two studies demonstrating the effect of the formulation applied directly to the test substrate were presented. Given the data available for the formulation as well as the parent triazoxide and metabolite M01, EFSA considers that the absence of any specific studies to demonstrate the effect of the soil metabolite M02 would not lead to a data gap.

A low risk to soil non-target micro-organisms was expected, based on the data presented and considering the representative use.

5.8. Risk to other non-target-organisms (flora and fauna)

According to the terrestrial guidance document (European Commission, 2002c) non-target plants are defined as non-crop plants located outside the treatment area. Given the representative use as a seed treatment, the treatment area would be confined to the in-field area, where seeds are drilled into the soil. Off-field contamination would thus be negligible during normal agronomic practice. The risk to non-target plants does not need to be assessed for seed treatment under the current risk assessment scheme. Still, a valid pre-emergence study was submitted. No visible phytotoxic effects were reported at exposure levels of 17.1 g triazoxide/ha (solo formulation "Triazoxide FS 050" exposed at approximately three times the representative dose rate).

5.9. Risk to biological methods of sewage treatment

A study on the effect of technical triazoxide on the rate of respiration in activated sludge was submitted. The EC_{50} for triazoxide was determined to be >10000 mg/L. Although concentrations of the test material were not verified by analysis, the study was considered to be of an acceptable quality, since the result for the toxic standard was within the expected range. The risk to biological methods of sewage treatment was considered to be low from the representative use.

6. Residue definitions

6.1. Soil

Definitions for risk assessment: triazoxide, M01 and M02

Definitions for monitoring: triazoxide

6.2. Water

6.2.1. Ground water

Definitions for exposure assessment: triazoxide, M01 and M02

Definitions for monitoring: triazoxide

6.2.2. Surface water

Definitions for risk assessment:

water:	triazoxide
sediment:	triazoxide, M01, M02 and M05
Definitions for monitoring:	triazoxide

6.3. Air

Definitions for risk assessment:	triazoxide
Definitions for monitoring:	triazoxide

6.4. Food of plant origin

Definitions for risk assessment:	triazoxide, M01 and M02
Definitions for monitoring:	triazoxide

6.5. Food of animal origin

Definitions for risk assessment:	Not proposed and not necessary
Definitions for monitoring:	Not proposed and not necessary

7. Overview of the risk assessment of compounds listed in residue definitions triggering assessment of effects data for the environmental compartments

7.1. Soil

Compound (name and/or code)	Persistence	Ecotoxicology
Triazoxide	High to very high persistent ($DT_{50\ lab\ (biphasic\ kinetic,\ overall)}$ = 208 – 278 d). ($DT_{50,\ field\ (biphasic\ kinetic,\ overall)}$ = 18 – 99 days, DT_{90} = 640 – 1080 days)	The acute and long-term risk to earthworms was considered to be low. The risk of triazoxide to soil non-target macro-organisms was assessed as low.
M01	Moderate persistent (decline $DT_{50\ lab}$ = 32.4 – 56.7 d)	The acute and long-term risk to earthworms was assessed to be low. The risk of M01 to soil non-target macro-organisms was assessed as low.
M02	High persistent (decline $DT_{50\ field}$ = 239 – 313 d)	The acute and long-term risk to earthworms was considered to be low. The risk of M02 to soil non-target macro-organisms was considered as low.

7.2. Ground water

Compound (name and/or code)	Mobility in soil	> 0.1 µg / L 1m depth for the representative uses (at least one FOCUS scenario or relevant lysimeter)	Pesticidal activity	Toxicological relevance	Ecotoxicological relevance
Triazoxide	low to medium mobile (K_{foc} = 245 – 1743 mL / g)	No	Yes	Yes	Yes
M01	slightly mobile (K_{foc} = 2053 – 4148 mL / g)	No	No	Yes	No
M02	low to medium mobile (K_{foc} = 385.6 – 1709.0 mL / g).	No	No	Yes	No

7.3. Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Triazoxide (surface water and sediment)	Triazoxide is very toxic to aquatic organisms. The risk to aquatic organisms from the representative use was considered to be low.
M01 (sediment only)	The risk from M01 to aquatic organisms, including *Chironomus* was considered to be low.
M02 (sediment only)	The risk from M02 to aquatic organisms was considered to be low.
M05 (sediment only)	The risk from M05 to aquatic organisms was considered to be low.

7.4. Air

Compound (name and/or code)	Toxicology
Triazoxide	Toxic by inhalation (LC_{50} 0.7 mg/L) Toxic: danger of serious damage to health by prolonged exposure through inhalation.

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

- Five batch data for the original source, analysed with a fully validated method of analysis or alternatively, reanalysis of the old batches with the new method (relevant for the representative uses evaluated, submission date proposed by the applicant: unknown; refer to chapter 1).

- Quality control data to support the technical specification for the additional source (relevant for the representative uses evaluated, submission date proposed by the applicant: data are available, however in view of Commission Regulation (EC) No 33/2008 these could not be considered in the peer review; refer to chapter 1).

- Validated analytical method for the active substance in air with a LOQ of 0.3 µg/m³ (relevant for the representative uses evaluated, submission date proposed by the applicant: unknown; refer to chapter 1).

- A refinement of the long-term risk assessment for granivorous mammals exposed to the spring use of triazoxide on barley seeds is required. This may also be required for the winter use in Member States where terrestrial vertebrates will be actively breeding during the autumn/winter (relevant for the representative uses evaluated, with the exception of autumn/winter use in Member States which would be outside the breeding season; submission date proposed by the applicant: unknown; refer to point 5.1).

CONCLUSIONS AND RECOMMENDATIONS

Overall conclusions

The conclusion was reached on the basis of the evaluation of the representative uses as a fungicide as proposed by the applicant for seed treatment on winter and spring barley, against several agriculturally important phytopathogens. Full details of the GAP can be found in the list of end points in Appendix A.

The representative formulated product for the evaluation was "Raxil S FS 040", a flowable concentrate for seed treatment (FS), containing 20 g/L triazoxide and 20 g/L tebuconazole.

The specification for the technical material should currently be regarded as provisional.

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.

Adequate methods are available to monitor all compounds given in the respective residue definitions in food/feed of plant origin, soil and water, however for the air a method validated to a LOQ of 0.3 µg a.s./m³ was identified as a data gap.

With regard to its toxicological properties, triazoxide was rapidly and extensively absorbed, but only partly bioavailable (50 %) to the target organ (blood system) due to its biokinetic properties. After single exposure it was shown to be toxic after oral or inhalative administration, but was not irritant or skin sensitizer. Consequently, the proposed classification for acute toxicity was **T, R23/25 'Toxic by inhalation and if swallowed'**.

After repeated oral or inhalative administration, the critical effect was the induction of haemolytic anaemia, with secondary effects in the spleen, liver, kidneys and bone marrow. The possible classification with Xn; R48/22 or T; R48/25 ('Harmful or Toxic: danger of serious damage to health by prolonged exposure if swallowed') could not be agreed by the experts, but the classification **T, R48/23 'Toxic: danger of serious damage to health by prolonged exposure through inhalation'** was proposed. Triazoxide was not considered to have a genotoxic potential and no carcinogenic

effects were observed in the long-term studies up to the highest doses tested. No specific adverse effects on fertility were shown in the multi-generation rat study, but the classification **R64 'May cause harm to breastfed babies'** was proposed, based on reduced pup survival during lactation that could be expected to result from the presence of triazoxide in milk. No developmental toxicity or teratogenic activity was observed in rats or rabbits.

The **acceptable daily intake** (ADI) is **0.0002 mg/kg bw/day,** based on the 2-year rat study and using a safety factor of 100, increased by an additional safety factor of 3. This was justified by the use of a lowest observed adverse effect level, the steep dose-response in the study and the absence of mechanistic information. The **acceptable operator exposure level** (AOEL) is **0.001 mg/kg bw/day,** based on the 90-day rat study, using a safety factor of 100 and a correction for bioavailability (50 %). The **acute reference dose** (ARfD) is **0.015 mg/kg bw,** based on the 4-week rat study and applying a safety factor of 100.

The dermal absorption values to be used in the risk assessment are 2.4 % for the concentrate and 2 % for the contaminated grain dust. The operator exposure estimates during the seed treatment are above the AOEL with the SeedTropex model, but realistic field studies show an exposure level up to 21 % of the AOEL with the use of coverall and gloves. Similarly, the exposure estimates for the worker loading and sowing treated seed are above the AOEL with the SeedTropex model, but below the AOEL considering a field study (26 %), with the use of long-sleeved shirt and long trousers. Bystander exposure is not expected to exceed the exposure of workers involved in loading/sowing treated seed (i.e. 26 % of the AOEL).

Based on the new metabolism study on barley conducted with seeds treated at a dose rate of 3 and 30 g a.s./100 kg seeds (N and 10N studies when compared to the cGAP), the residue was defined as triazoxide alone for monitoring and as sum of triazoxide, M01 and M02 for risk assessment. A conversion factor of 6 was proposed for risk assessment derived from the metabolism study, taking into account the respective percentage at which each compound was detected in straw.

A new residue data set was submitted where the samples were analysed using an analytical method achieving a LOQ of 0.001 mg/kg, and the MRL for barley grain was proposed at the LOQ value. Such an unusually low value was proposed, given the low ADI agreed for the parent compound. The residue data are supported by the storage stability study showing triazoxide residues to be stable up to 2 years when stored frozen at -18°C. Processing studies were not submitted and are not required. In addition, the available data are sufficient to conclude that significant residues are not expected to be present in rotational crops.

Estimated intakes by animals were calculated to be below the trigger value of 0.1 mg/kg DM. A goat metabolism study was however provided in order to confirm that transfer of residues in animal matrices is not expected at levels that could be of concern for the consumers. Since the TRRs in goat matrices were shown to be below 0.0005 mg/kg when expressed on a 1N rate basis, the setting of a residue definition and proposing MRLs for animal matrices were considered not necessary.

No chronic or acute risks were identified for the consumers, with the TMDI being less that 4 % of the ADI and the IESTI less that 0.1 % of the ARfD when calculations are performed using the EFSA PRIMo model, the proposed MRL of 0.001 mg/kg for barley, and the conversion factor of 6.

Triazoxide may be considered to be high to very high persistent in soil under dark aerobic conditions at 20°C ($DT_{50\ lab\ (biphasic\ kinetic,\ overall)}$ = 208 – 278 days). The degradation of triazoxide proceeds either through reduction to M01, or through production of M02. The assessment based on the decline from the peak observed indicated that metabolite M01 was moderately persistent in soil ($DissT_{50\ lab}$ = 32.4 – 56.7 days), and metabolite M02 could be considered highly persistent (decline M02 $DissT_{50\ field}$ = 239 – 331 days; excluding the UK field trial where no decline is observed). Unextracted residues amounted to a maximum of 29.8 % AR after 120 days (end of the study). Mineralization was practically negligible in the four soils tested.

Photolysis slightly enhances degradation of triazoxide in soil, but it is not expected to contribute significantly to its environmental dissipation.

Following the recommendation of FOCUS kinetics (FOCUS, 2006) a kinetic analysis of the field dissipation data to derive degradation rates and formation fractions of the parent compound and the metabolites was provided within the resubmission application. PEC soil were calculated for triazoxide and its soil major metabolites following standard procedures.

According to the available studies, triazoxide may be considered as low to medium mobile in soil (K_{foc} = 245 – 1743 mL /g), metabolite M01 may be considered slightly mobile (K_{foc} = 2053 – 4148 mL /g), and metabolite M02 may be considered low to medium mobile (K_{foc} = 385.6 – 1709.0 mL /g). The narrow range of pH and the ionisable character of the metabolite M02 were noted. Whereas a large margin of safety is considered to exist for the representative use, further data could be needed if other uses at significantly higher application rates are applied for in the future.

Triazoxide was stable to hydrolysis at pH 4, practically stable at pH 7, and readily hydrolysed at pH 9 (DT_{50} = 6.6 days). The main hydrolysis metabolite was M04. Triazoxide is rapidly photolysed in water (DT_{50} = 24.4 hours equivalent to 3.5 natural solar days at 33 ºN). An additional study indicated that the photolysis half-life of triazoxide in water is expected to range from 1.7 to 9.7 days, depending on the season and the latitude (30 – 50 ºN).

No ready biodegradability study is available and therefore triazoxide is considered not readily biodegradable.

In aquatic water / sediment systems, triazoxide dissipated rapidly from water to sediment phase, and broke down to form the metabolites M01 and M05. Unextractable residues in the sediment amounted up to 55.7 % AR in the sediment after 91 days. Mineralization was negligible in both systems. The limited sampling regime of these experiments prevents the calculation of reliable kinetic parameters. However, a simple non-linear kinetic analysis was presented by the applicant to derive dissipation and degradation rates of triazoxide and metabolite M01 in the water sediment systems. This kinetic analysis was only partially validated (only whole system results for the Lienden system were confirmed). For the IJzendoorn system, no reliable whole system half-lives for the parent compound and metabolite M01 were obtained due to poor fit. Worst-case whole system half-lives of 4.3 days and 323 days were estimated for triazoxide and metabolite M01, respectively, based on results of Lienden system.

The necessary surface water and sediment exposure assessments (PEC) were carried out for triazoxide as well as the metabolites M01, M02 and M05 using the FOCUS step 1, step 2 and step 3 approach. For the metabolites M01 and M05 the available step 1 and step 2 values are relied on for the risk assessment. Detailed information about model parameterisation is provided in the list of end points in Appendix A.

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (FOCUS, 2000) scenarios and models (PEARL 3.3.3 and PELMO 3.3.2) for the active substance triazoxide and the metabolites M01 and M02. To assess the risk associated with preferential transport through structured soils the Chateaudun scenarios were also simulated using the MACRO model. The potential for groundwater exposure from the representative uses for these compounds above the parametric drinking water limit of 0.1 µg/L was concluded to be low in geoclimatic situations represented by all relevant FOCUS groundwater scenarios.

Triazoxide is not expected to significantly volatilize or to be subject to long-range transport in air.

The first-tier short-term TER values for granivorous birds were above the Annex VI trigger values, indicating a low risk. The margin of safety (TER=23.5) was considered to cover the uncertainty related to the derivation of a short-term toxicity end point, due to food avoidance (end point based on consumption in group where there was 30 % mortality). Further refinements were required to address

the acute and long-term risk to birds. Based on yellowhammer as focal species, the acute TER value was calculated to be 9.1. Yellowhammer would have to consume 159 (including a 10-fold uncertainty factor) seeds on an acute time scale to breach the Annex VI trigger. This number of seeds would cover approximately 3.45 m^2 of a field, and the number of seeds would cover 90 % of the daily food requirement of a yellowhammer. Furthermore, worst-case field studies indicated that yellowhammer could consume 1/3 of the critical number of seeds in one feeding event. Given these facts, in addition to the indication of food avoidance behaviour detected in the short-term dietary study, it was concluded that the risk to granivorous birds from consumption of treated seeds could be considered to be low on an acute timescale. The conclusion was supported by an additional assessment for a fast-feeding granivorous bird like the woodpigeon. A long-term risk assessment on reproductive birds was considered relevant for the spring use of triazoxide as a seed treatment. A refined long-term TER of 2.23 was calculated based on residue decline data for triazoxide in barley seed on soil surface. Further refinements were needed to address the long-term risk to granivorous birds from the spring use. Following the initial risk assessment, further data and refinements were considered during the resubmission. Four species were identified as focal species (skylark, chaffinch, woodpigeon and yellowhammer) in the Additional Report. Further information was provided supporting the proportion of the food obtained in the treated area (PT) for each focal species as well as the proportion of food types obtained from the treated crop (PD). The refined TER values were above the Annex VI trigger values for all representative focal species, therefore the long-term risk to granivorous birds for both the use in autumn and spring sown barley was assessed as low.

The tier 1 acute risk assessment for granivorous mammals was found to be low. Further refinements were required with regard to the long-term risk assessment for granivorous mammals. The refinements in the original review were based on wood mouse as focal species and on use of measured residue data, however they were considered as not satisfactory and further refinements were required to address the long-term risk to granivorous mammals. During the resubmission application further data were provided to refine the risk assessment. However, the higher tier risk assessment gave a TER_{lt} below the Annex VI trigger value, indicating a potential high long-term risk. Therefore, the long-term risk assessment for granivorous mammals needs further refinements and a data gap remains. The issue has been indicated as a critical area of concern.

Risk assessment of secondary poisoning and consumption of contaminated water was considered not relevant.

Triazoxide is proposed to be classified as very toxic to aquatic organisms. The acute and chronic risk to aquatic organisms was considered to be low. Furthermore, the risk to sediment-dwelling organisms from the metabolites M01, M02 and M05 was considered as low.

The acute risk to earthworms was considered to be low. The long-term risk from triazoxide and the soil metabolites M01 and M02 to earthworms was considered as low. Concerning other soil non-target macro-organisms, the risk to springtails was considered low for all potential soil residues. In addition, the potential risk from triazoxide and its metabolites to soil litter degradation processes was assessed as low.

The risk to bees and non-target arthropods was assessed to be low, as was the risk to soil non-target micro-organisms, biological methods of sewage treatment, and non-target plants.

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

- Barley seed treatments at application rate equivalent to 6 g a.s./ ha is the only use assessed at EU level. To assess other uses, it is expected that a considerable amount of studies would be triggered, including Annex II data that would result in new EU level end points.

- Use of personal protective equipment (coverall and gloves) by the operators treating seed, and use of long-sleeved shirt and long trousers by the workers loading/sowing the treated seed are necessary in order to have exposure levels below the AOEL.

- In the risk assessment for granivorous birds it was suggested that spillages could be risk managed using appropriate labelling/user awareness campaigns to reduce the foraging of granivorous birds. As a consequence, birds would have to forage more in order to locate treated seeds, which in effect would increase the time over which consumption occurred, and increase the potential for metabolism and excretion of any ingested triazoxide following consumption of treated barley seed.

ISSUES THAT COULD NOT BE FINALISED

None.

CRITICAL AREAS OF CONCERN

- A potential high long-term risk was indicated for granivorous mammals, therefore the long-term risk assessment needs further refinement.

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APPENDICES

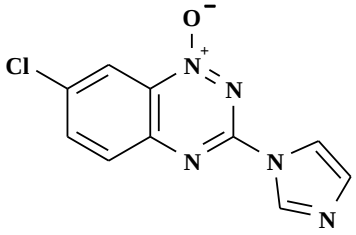
APPENDIX A – LIST OF END POINTS FOR THE ACTIVE SUBSTANCE AND THE REPRESENTATIVE FORMULATION

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

Active substance (ISO Common Name) ‡	Triazoxide
Function (*e.g.* fungicide)	Fungicide

Rapporteur Member State	UK
Co-rapporteur Member State	-

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	7-chloro-3-imidazol-1-yl-1,2,4-benzotriazine 1-oxide
Chemical name (CA) ‡	7-chloro-3-(1*H*-imidazol-1-yl)-1,2,4-benzotriazine 1-oxide
CIPAC No ‡	729
CAS No ‡	72459-58-6
EC No (EINECS or ELINCS) ‡	276-668-4
FAO Specification (including year of publication) ‡	FAO specification is not available
Minimum purity of the active substance as manufactured ‡	970 g/kg
Identity of relevant impurities (of toxicological, ecotoxicological and/or environmental concern) in the active substance as manufactured	Toluene, max. 3 g/kg
Molecular formula ‡	$C_{10}H_6ClN_5O$
Molecular mass ‡	247.7 g/mol
Structural formula ‡	

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

Physical and chemical properties (Annex IIA, point 2)

Melting point ‡	177-181°C (99.7%)
Boiling point ‡	Not measured, decomposition above 170°C
Temperature of decomposition ‡	Decomposition occurs at 170°C (98.2%) technical material
Appearance ‡	Yellow/light greenish powder (99.7%) Yellow/green crystalline solid (97%)
Vapour pressure ‡	1 x 10^{-7} Pa at 20 °C (99%)
Henry's law constant ‡	7 x 10^{-7} Pa m^3 mol^{-1} at 20 °C
Solubility in water (state temperature, state purity and pH) ‡	0.058 g/L at 20°C (4 pH) (99.7%) 0.034 g/L at 20°C (5-9 pH) (99.7%)
Solubility in organic solvents ‡	acetone 5.3 g/l at 20°C (99%) acetonitrile 4.2 g/l at 20°C (99%) dichloromethane 32 g/l at 20°C (99%) dimethylformamide 20 g/l at 20°C dimethylsulfoxide 14 g/l at 20°C ethanol/PEG (1:1) 4.9 g/l at 20°C hexane 0.05 g/l at 20°C 1-octanol 2.3 g/l at 20°C polyethylene glycol 4.1 g/l at 20°C 2-propanol 1.8 g/l at 20°C toluene 6.9 g/l at 20°C
Surface tension ‡	71.9 mN/m at 20°C (90 % saturated solution) (98.2%)
Partition co-efficient ‡	log $P_{O/W}$ = 2.04 at 23°C (99%) [The solubility in water did not alter between pH 5 and pH 9, therefore the full range of pH was not examined.] Test carried out in de-ionized water (pH not stated)
Dissociation constant (state purity) ‡	Triazoxide is a very weak base, which can only be completely protonised in non-aqueous systems in the presence of very strong acids. It is not possible to specify a pK value for water.
UV/VIS absorption (max.) incl. ε	UV absorb 262 nm (ε = 49400 l mol^{-1} cm^{-1}) UV absorb ≈380 nm (ε = ≈5000 l mol^{-1} cm^{-1}) (99.8%)
Flammability ‡	Not considered highly flammable (99.1%)
Explosive properties ‡	Non-explosive (99.1%)
Oxidising properties ‡	Oxidising (99.1%)

Summary of representative uses evaluated (*Triazoxide*)*

Crop and/ or situation (a)	Member State or Country	Product name(s)	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)	Concentration of a.s. (i)	Method kind (f-h)	Growth stage & season (j)	No. of application min/max (k)	Interval between applications (min)	% Product min/max (n)	Water [L/ha] min/max	g a.s./dt seed min/max		
Cereals: barley	UK, Belgium, Austria, Poland, Slovakia	Raxil S FS 040	F	barley leaf stripe, seed-borne net blotch, smuts	FS	20 g/L triazoxide, 20 g/L tebuconazole	seed dressing	winter & spring	1	n.a.	n.a.	n.a.	2 - 3 (per/ha rate depends on seed rate; max. 6 g a.s./ha)	n.a.	Raxil S FS 040 is a mixture with tebuconazole [1]

n.a. not applicable

[1] A potential high long-term risk was indicated for granivorous mammals.

* For uses where the column "Remarks" is marked in grey further consideration is necessary. Uses should be crossed out when the notifier no longer supports this use(s).

(a) For crops, the EU and Codex classifications (both) should be taken into account; where relevant, the use situation should be described (e.g. fumigation of a structure)

(b) Outdoor or field use (F), greenhouse 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, drench

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

(i) g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxypyr). **In certain cases, where only one variant is synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).**

(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) Indicate the minimum and maximum number of application possible under practical conditions of use

(l) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha

(m) PHI - minimum pre-harvest interval

Methods of Analysis

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

Technical as (analytical technique)	Triazoxide was determined in the technical active substance and plant protection product by HPLC-DAD [identification was based on H^1NMR].
Impurities in technical as (analytical technique)	Organic impurities were determined by HPLC- HPLC-DAD [identification was based on H^1 and C^{13} NMR] (limit of determination was 0.1%).
Plant protection product (analytical technique)	Triazoxide in the plant protection product was determined by reverse phase HPLC-DAD.

Analytical methods for residues (Annex IIA, point 4.2)

Residue definitions for monitoring purposes

Food of plant origin		Triazoxide
Food of animal origin		Residue definition for animal products was not proposed as positive residues were not expected in animal products
Soil		Triazoxide
Water	surface	Triazoxide
	drinking/ground	Triazoxide
Air		Triazoxide
Body fluids and tissues		Triazoxide

Monitoring/Enforcement methods

Food/feed of plant origin (analytical technique and LOQ for methods for monitoring purposes)	Triazoxide residues in plant and plant products were determined by extraction with acetone/water and the resulting extracts clean up on XTR-cartridges and the resulting eluants analysed by HPLC-MS/MS. The limit of determination was 0.001 mg/kg for barley grain and straw, orange, tomato, and rape seed and pea seed (0.05 mg/kg for barley foliage)
Food/feed of animal origin (analytical technique and LOQ for methods for monitoring purposes)	Triazoxide residues in animal products were determined by extraction with acetone/water (milk, muscle and fat) and the resulting extracts clean up on XTR-cartridges and for liver kidney and eggs extracted with acetonitrile only. The resulting extracts were analysed by HPLC-MS/MS. The limit of determination was 0.001 mg/kg (milk, muscle, fat, liver, kidney and eggs). Methods not required.
Soil (analytical technique and LOQ)	Triazoxide (and its metabolites M01 and M02) residues in soil were determined by extraction with acetonitrile/water and the resulting extracts analysed by HPLC-MS/MS. The limit of determination was 0.001 mg/kg.

Water (analytical technique and LOQ)	Triazoxide (and its metabolite M01) residues in water were determined after acidification, by direct injection into a HPLC-MS/MS. The limit of determination was 0.1 µg/l for surface water.
Air (analytical technique and LOQ)	Triazoxide residues in air were determined using a Tenax adsorption tube, by drawing air through the tube at 2 l/min for a period of 6 hours. The tubes were then extracted with acetonitrile and resulting extracts analysed by HPLC-UV. The limit of determination was 0.6 µg/m^3. Method with a limit of determination of 0.3 µg/m^3 is required.
Body fluids and tissues (analytical technique and LOQ)	Triazoxide residues in blood were determined by extraction with acidified acetonitrile and the resulting extracts centrifuged (to remove protein). The resulting supernatants were diluted with water and analysed by HPLC-MS/MS. The limit of determination was 0.05 mg/l.

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

	RMS/peer review proposal
Active substance	Oxidising (O) Contact with combustible material may cause fire (R8)

Impact on Human and Animal Health:

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

Rate and extent of oral absorption ‡	Rapid with more than 80 % of the dose excreted within 24 hours (max plasma concentrations at 20-90 minutes) via urine and bile. Only 50 % considered available to the target tissues, by excluding bile excretion (~43 %) during the first 4 hours (first pass metabolism).
Distribution ‡	Widespread with the highest levels in liver and kidney.
Potential for accumulation ‡	No evidence of accumulation at 72 hours; some evidence that the decline in radioactivity was slower from blood compared to other tissues.
Rate and extent of excretion ‡	Rapid, with more than 80 % of the dose eliminated within 24 hours via bile (64-75 %), urine (26-30 %) and faces (<10 %)
Metabolism in animals ‡	Mainly by deoxygenation, cleavages (mainly of the imidazole ring, minimal cleavage of the benzotriazine ring structure) and conjugations.
Toxicologically relevant compounds ‡ (animals and plants)	Triazoxide and metabolites
Toxicologically relevant compounds ‡ (environment)	Triazoxide and metabolites

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral ‡	98 mg/kg bw	R25
Rat LD_{50} dermal ‡	>5000 mg/kg bw	
Rat LC_{50} inhalation ‡	0.7 mg/l (4 hour exposure, primarily nose).	R23
Skin irritation ‡	Non-irritant	
Eye irritation ‡	Non-irritant	
Skin sensitisation ‡	Negative (M & K test)	

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect ‡	Red blood system (reduced RBC parameters, RBC inclusions and morphological changes) with secondary effects in the spleen (darkly coloured, increased haematopoiesis, congestion and atrophy of follicles), liver (enzyme induction and bile proliferation) and bone marrow (darkly coloured, increased haematopoiesis). Increased weight and ionized iron in the spleen, liver and kidneys.	
Relevant oral NOAEL ‡	0.21 mg/kg bw/day (3-month rat) 0.4 mg/kg bw/day (1-year dog)	R48[16]
Relevant dermal NOAEL ‡	35 mg/kg bw/day (adjusted for 5 days/week exposure)	
Relevant inhalation NOAEC ‡	0.008 mg/L air	R48/23

Genotoxicity ‡ (Annex IIA, point 5.4)

Equivocal findings in some studies but the weight of evidence indicates that triazoxide is not genotoxic *in vivo.*	

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

Target/critical effect ‡	Spleen (darkly coloured)	
Relevant NOAEL ‡	0.05 mg/kg bw/day (LOAEL, 2-year rat) 0.3 mg/kg bw/day (NOAEL, 21-month mouse)	
Carcinogenicity ‡	No carcinogenic potential up to the highest dose tested (25 ppm)	

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction toxicity

Reproduction target / critical effect ‡	Parental: increased organ weight (spleen, ovaries) Offspring: reduced pup survival during lactation Reproductive: no adverse effects	R64
Relevant parental NOAEL ‡	0.11 mg/kg bw/day	
Relevant reproductive NOAEL ‡	2 mg/kg bw/day (highest dose tested)	
Relevant offspring NOAEL ‡	0.11 mg/kg bw/day	

Developmental toxicity

Developmental target / critical effect ‡	None identified up to the highest dose tested	
Relevant maternal NOAEL ‡	3 mg/kg bw/day (rat) 10 mg/kg bw/day (rabbit)	

[16] R48/22 or R48/25 to be considered by EChA

Relevant developmental NOAEL ‡	10 mg/kg bw/day (rat and rabbit)	

Neurotoxicity (Annex IIA, point 5.7)

Acute neurotoxicity ‡	No data, not necessary	
Repeated neurotoxicity ‡	No data, not necessary	
Delayed neurotoxicity ‡	No data, not necessary	

Other toxicological studies (Annex IIA, point 5.8)

Mechanism studies ‡	None
Studies performed on metabolites or impurities ‡	None

Medical data ‡ (Annex IIA, point 5.9)

No human poisoning incidents are known to the applicant and no detrimental health effects or long-term damage have been observed among employees.

Summary (Annex IIA, point 5.10)	Value	Study	Safety factor
ADI ‡	0.0002 mg/kg bw/day	2-year rat	300*
AOEL ‡	0.001 mg/kg bw/day	90-d rat, supported by the multigeneration study	overall 200**
ARfD ‡	0.015 mg/kg bw	28-day rat	100

* including an additional factor of 3 for using a LOAEL, the steep dose response and the absence of mechanistic information

** including the correction for 50 % bioavailability

Dermal absorption ‡ (Annex IIIA, point 7.3)

Formulation (‘Raxil S FS 040’)	2.4 % for the concentrate 2 % for contaminated grain dust

Exposure scenarios (Annex IIIA, point 7.2)

Operator	Scenario: seed treatment with ‘Raxil S FS 040’ with use of PPE (coverall and gloves)	
	Model/Study	Exposure (% AOEL)
	Seed Tropex (UK)	380
	Seed Tropex (refined)	123
	Field study	up to 21

Workers	Scenario: loading/sowing of seed treated with 'Raxil S FS 040' (with the use of coverall in the model and single layer of clothing (long-sleeved shirt, long trousers) in field study)	
	Model/Study	Exposure (% AOEL)
	Seed Tropex (UK)	500
	Seed Tropex (refined)	300
	Field study	26
Bystanders	Not expected to exceed the exposure of workers loading/sowing treated seed (26 % of AOEL).	

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

	RMS/peer review proposal
Substance classified (name)	Toxic by inhalation and if swallowed (T, R23/25) Toxic: danger of serious damage to health by prolonged exposure through inhalation (T, R48/23) Danger of serious damage to health by prolonged exposure if swallowed (R48/22 or R48/25*) May cause harm to breastfed babies (R64)

* to be confirmed by EChA

Residues

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

Plant groups covered	Cereals (Barley, seed treatment)
Rotational crops	Clover, Turnips
Metabolism in rotational crops similar to metabolism in primary crops?	No assessment could be made as no characterisation of the residue was attempted due to low total [^{14}C] residues at harvest (<0.05 mg/kg) in both studies.
Processed commodities	No data submitted and not required.
Residue pattern in processed commodities similar to residue pattern in raw commodities?	Not applicable.
Plant residue definition for monitoring	Triazoxide
Plant residue definition for risk assessment	Triazoxide and its metabolites M01 and M02
Conversion factor (monitoring to risk assessment)	6, derived from the ratios of triazoxide, M02 and M01 in barley straw in the metabolism study (2.1/4.0/5.9)

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

Animals covered	Goat
Time needed to reach a plateau concentration in milk and eggs	2 days
Animal residue definition for monitoring	Residue definition for animals was not proposed as positive residues are not expected in animal products.
Animal residue definition for risk assessment	Residue definition for animals was not proposed as positive residues are not expected in animal products.
Conversion factor (monitoring to risk assessment)	Not applicable.
Metabolism in rat and ruminant similar (yes/no)	No characterisation work was undertaken due to the total [^{14}C] residues indicating that positive residues are not expected in animal products.
Fat soluble residue: (yes/no)	No (based on partition coefficient)

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

Based on radiolabel study, residues greater 0.001 mg/kg are not expected.

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

Triazoxide residues of stable up to 24 months in barley forage, straw and grain when stored frozen at -18°C.

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

	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)	No <0.01 mg/kg diet	No	No
Potential for accumulation (yes/no):	No	n/a	n/a
Metabolism studies indicate potential level of residues ≥ 0.01 mg/kg in edible tissues (yes/no)	<0.0005 mg/kg[a]	n/a	n/a
	Feeding studies (Specify the feeding rate in cattle and poultry studies considered as relevant). **No study available.** Residue levels in matrices: Mean (max) mg/kg		
Muscle	-	-	-
Liver	-	-	-
Kidney	-	-	-
Fat	-	-	-
Milk	-		
Eggs		-	

[a]: TRRs <0.01 mg/kg in fat and muscle, 0.02 mg/kg in milk, 0.13 mg/kg in kidney and 0.26 mg/kg in liver in a goat metabolism study conducted at a rate of 4.3 mg/kg DM (*c.a.* 1000 N and 600 N for dairy and beef cattle respectively). Consequently, TRRs (and individual compounds) are not expected to be above 0.0005 mg/kg when levels are expressed on a 1N rate basis.

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 Southern Region field or glasshouse	Trials results relevant to the representative uses (a)	Recommendation/comments	MRL estimated from trials according to representative use	HR (mg/kg) (c)	STMR (mg/kg) (b)
Barley, wheat, oat and rye	Northern Field	18x <0.05 (grain) 18x <0.05 (straw)	Data set not considered appropriate to propose MRL, since analyses conducted with an inappropriate LOQ of 0.05 mg/kg.	-	0.05 0.05	0.05 0.05
Barley	Northern Field	4x <0.001 (grain) 4x <0.001 (straw)	Additional trials not required given the no-residue situation.	0.001	0.001 Grain and straw	0.001 Grain and straw
	Southern Field	2x <0.001 (grain) 2x <0.001 (straw)				

(a) Numbers of trials in which particular residue levels were reported *e.g.* 3 x <0.01, 1 x 0.01, 6 x 0.02, 1 x 0.04, 1 x 0.08, 2 x 0.1, 2 x 0.15, 1 x 0.17

(b) Supervised Trials Median Residue *i.e.* the median residue level estimated on the basis of supervised trials relating to the representative use

(c) Highest residue

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

ADI	0.0002 mg/kg bw/day
TMDI (% ADI) according to EFSA PRIMo model	< 4 % ADI for all the diets included in the PRIMo model.
TMDI (% ADI) according to national diets	-
IEDI (WHO European Diet) (% ADI)	-
NEDI (% ADI)	-
Factors included in IEDI and NEDI	MRL for barley and CF of 6
ARfD (mg/kg bw/d)	0.015 mg/kg bw
IESTI (% ARfD) according to EFSA PRIMo model	Less than 0.1 %
NESTI (% ARfD) according to national (to be specified) large portion consumption data	-
Factors included in IESTI and NESTI	MRL for barley and CF of 6

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 study submitted and not required.	-	-	-	-

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

Barley	0.001* mg/kg

When the MRL is proposed at the LOQ, this should be annotated by an asterisk (*) after the figure.

Environmental fate and behaviour

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

Mineralization after 100 days ‡	0.1 % AR after 91-120 d, [^{14}C-phenyl]-triazoxide (n = 4 soils) Sterile conditions: n.a.
Non-extractable residues after 100 days ‡	18.9 - 29.8 % AR after 91-120 d, [^{14}C-phenyl]-triazoxide (n= 4 soils) Sterile conditions: n.a.
Metabolites requiring further consideration ‡ - name and/or code, % of applied (range and maximum)	**M01** In laboratory study with [^{14}C-phenyl]-label max. 12.8 % AR after 30 d, (n= 4 soils, molar basis). In field dissipation study: max. 17.7 % applied after 539 d (Italian trial, molar basis). **M02** In laboratory study with [^{14}C-phenyl]-label: max. 9 % AR after 3 d, (individual replicate 10.2 % AR, n= 4 soils, molar basis). In field dissipation study: max. 18.7 % applied after 14 and 140 d (Italian trial, molar basis).

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

Anaerobic degradation ‡

Mineralization after 100 days	0.3 - 0.4 % AR after 90-120 d, (60-90 d after flooding), [^{14}C-phenyl]-triazoxide (n= 1 soil). max. 0.7 % AR after 41d, (11 d after flooding) [^{14}C-phenyl]-triazoxide (n= 1 soil) Sterile conditions: n.a.
Non-extractable residues after 100 days	28.1 % AR after 120 d, (90 d after flooding), [^{14}C-phenyl]-triazoxide (n= 1 soil). max. 32.4 % AR after 90 d, (60 d after flooding) [^{14}C-phenyl]-triazoxide (n= 1 soil).
Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	**M01** Max. 25.5 % AR after 155 d (125 d after flooding, end of study)

Soil photolysis ‡

Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	None

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

Laboratory studies ‡

Parent	Aerobic conditions					
Soil type	pH	t °C / % MWHC	DT_{50} (d) First order bi-phasic:	DT_{50} (d) overall	St. (r^2)	Method of calculation
Höfchen am Hohenseh Silt	7.6	20°C /45%	33.3 [a] 498 [b]	258	0.99	bi-phasic (first order two compartment, FOTC)
Laacher Hof AIII Silt loam	7.4	20°C /45%	7.1 [a] 412 [b]	278	0.99	
BBA 2.1 Sand	5.9	20°C /45%	26.5 [a] 370 [b]	259	0.93	
Laacher Hof AXXa Sandy loam	7.2	20°C /45%	9. 2 [a] 404 [b]	208	0.99	
Geometric mean			15.5 [a] 419 [b]	250		

[a] 1st phase
[b] 2nd phase

M01	Aerobic conditions						
Soil type	pH	t °C / % MWHC	DT_{50}/ DT_{90} (d)	Peak %	DT_{50} (d) 20 °C pF2/10kPa	St. (r^2)	Method of calculation
Höfchen am Hohenseh Silt	7.6	20°C /45%	(a) 29.9 / 99.5 *(b) 347.1/ 1152.9**	12.8	(a) 18.9	(a) 0.99 *(b) 0.34**	See footnotes (a) and (b)
Laacher Hof AIII Silt loam	7.4	20°C /45%	(a) 6.6/ 21.9 *(b) 56.7/ 188.4*	9.4	(a) 4.4	(a) 0.99 *(b) 0.89*	
BBA 2.1 Sand	5.9	20°C /45%	(a) 10 / 33.1 *(b) 45.2/ 150.2*	9.5	(a) 9.3	(a) 0.93 *(b) 0.82*	
Laacher Hof AXXa Sandy loam	7.2	20°C /45%	(a) 4.7/ 15.8 *(b) 32.4/ 107.7*	10.2	(a) 3.5	(a) 0.99 *(b) 0.8*	
Geometric mean			(a) 9.8/ 32.7 *(b) 44/ 145*		7.2		

** poor fit, not included in mean, not considered reliable for risk assessment.*
(a) Box model. Parent bi-phasic (DFOP), M01 SFO (f.f. form parent = 1)
(b) SFO non-linear regression analysis of data from the peak (n=3)

Field studies ‡

Parent	Aerobic conditions								
Soil type (application to bare soil, subsequently incorporated and cropped).	Location (country or USA state)	pH	Depth (cm)	DT_{50} (d) actual	DT_{90}(d) actual	St. (r^2)‡	DT_{50} (d) Norm.	χ^2 (%)†	Method of calculation
Sandy loam	UK	8.4	0-30	48	640	0.933	a)1.88 b)70.4	12.4	Time-step normalised to 20ºC and pF2 (Q_{10} = 2.58) HS kinetic fits used in all cases (normalised and un-normalised fits)
Silt loam	Germany	7.4	0-30	99	851	0.930	a)not reliable b) 100.5	10.4	
Silt loam	S. France	8.7	0-30	18	705	0.951	a)5.21 b)119.5	12.3	
Silt loam	Italy	8.2	0-30	29	1080	0.915	a)4.94 b)173.3	12.3	
Geometric mean				40	802		a)3.63 b)110.0		

‡St. given for actual data
†χ^2 given for timestep normalised data
a) fast phase of HS
b) slow phase of HS

M02		Aerobic conditions								
Soil type	Location	pH	Depth (cm)	DT_{50} (d) actual[#]	DT_{90} (d) actual	St. (r^2)‡	DT_{50} (d) Norm.	kinetic f.f.	χ^2 (%)†	Method of calculation
Sandy loam	UK	8.4	0-30	not reliable	n.c.	0.95	not reliable	-	-	[#]Actual: SFO decline after the max. observed. [a] apparent conservative value calculated from decline from maximum residue [b]Normalised: ModelMaker formation and degradation. Parent HS: M02 SFO normalised to 20°C/ 100% FC (B.8.1.3.c)
Silt loam	Germany	7.4	0-30	239	n.c.	0.95	86[a]	-[a]	6.5	
Silt loam	S. France	8.7	0-30	313	n.c.	0.76	46[b]	0.258	40.5	
Silt loam	Italy	8.2	0-30	296	n.c.	0.68	95[b]	0.324	20.0	
Geometric mean				280.8	-	-	72	-	-	
maximum				-	-	-	-	0.324	-	

n.a = not applicable n.c. = not calculated
‡St. given for actual data
†χ^2 given for time step normalised data

pH dependence ‡ (yes / no) (if yes type of dependence)	Triazoxide, M01 and M02: No
Soil accumulation and plateau concentration ‡ From calculations at B.8.3.1.	**Triazoxide:** Peak plateau concentration of 0.0148 mg/kg reached after 10 years application of 6 g a.s./ha per annum. (Steady state concentration 0.0068 mg/kg). Assuming 5 cm soil depth, application rate 6 g a.s./ha, pseudo 1st order DT_{50} of 325.3 d, soil density 1.5 g/cm^3). **M01:** Not required as laboratory DT_{90} values for M01 <1 year. **M02:** Peak plateau concentration of 0.002698 mg/kg reached after 7 years. (Steady state concentration 0.001202 mg/kg). Assuming max. formation 18.7 % applied (molar basis) of application rate 6 g a.s/ha = 1.122 g/ha (worst-case non-normalised field DT_{50} of 313 d, 5 cm soil depth and soil density 1.5 g/cm$^{3)}$

Laboratory studies ‡

Parent	Anaerobic conditions					
Soil type	pH	t °C / % MWHC	DT_{50} / DT_{90} (d)	DT_{50} (d) 20 °C pF2/10kPa	St. (r^2)	Method of calculation
Höfchen am Hohenseh Silt	7.6	20°C / 45%	137.1/ 455.5 (anaerobic phase only)	n.a.	0.96	SFO (non-linear regression)

M01	Anaerobic conditions						
Soil type	pH	t °C / % MWHC	DT_{50}/ DT_{90} (d)	Peak %	DT_{50} (d) 20°C pF2/10kPa	St. (r^2)	Method of calculation
Höfchen am Hohenseh Silt	7.6	20°C / 45%	n.c.	25.5*	n.a.	n.a	n.a.

n.a. not applicable. n.c. not calculated. *Maximum amount of M01 was at study end.

Soil adsorption/desorption (Annex IIA, point 7.1.2)

Parent ‡							
Soil Type	OC %	Soil pH	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
BBA. 2.1 sand	0.95	5.6	-	-	3.67	386	0.7457
BBA 2.2. loamy sand	2.42	5.4	-	-	5.93	245	0.7871
BB 2.3 sandy loam	1.14	5.8	-	-	3.64	319	0.7848
Höfchem am Hohenseh silt	2.11	6.7	–	–	38.8	1743	0.7682

Arithmetic mean		**673**	**0.7715**
pH dependence, Yes or No	No		

M01 ‡							
Soil Type	OC %	Soil pH	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Höfchem am Hohenseh silt	2.11	6.7	-	-	43.3	2053	0.7379
Laacher Hof AIII silt loam	0.83	6.5	–	–	21.3	2571	0.7066
Laacher Hof AXXa sandy loam	1.02	6.3	–	–	42.3	4148	0.7567
Arithmetic mean						**2924**	**0.7337**
pH dependence (yes or no)			No				

M02 ‡							
Soil Type	OC %	Soil pH	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Höfchem am Hohenseh silt	2.62	6.1	-	-	10.10	385.6	0.7464
Laacher Hof AIII silt loam	1.10	6.4	–	–	18.8	1709.0	0.8097
Laacher Hof AXXa sandy loam	1.3	6.0	–	–	10.95	842.4	0.7480
Arithmetic mean						**979**	**0.7680**
pH dependence (yes or no)			Narrow range of soil pH tested (6 - 6.4). M02 is a base so it is possible sorption may be affected by pH. However, PECgw was <0.001 µg/kg and considered sufficiently worst-case with a wide margin of safety.				

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

Column leaching ‡	No data submitted. None required.
Aged residues leaching ‡	No data submitted. None required.
Lysimeter/ field leaching studies ‡	No data submitted. None required.

PEC (soil) (Annex IIIA, point 9.1.3)

Parent

Method of calculation	DT_{50} (d): 325.3 days Kinetics: pseudo first order Field or Lab: worst-case DT_{90} from the field dissipation trial of 1080 days (before normalisation) divided by 3.32
Application data	Crop: barley seed Depth of soil layer: 5 cm Soil bulk density: 1.5 g/cm^3 % plant interception: Seed treatment so no crop interception. Number of applications: 1 Interval (d): n.a. Application rate(s): 6 g a.s./ha (3 g a.s./100 kg seed, sowing rate 200 kg/ha)

$PEC_{(s)}$ (mg/kg)		Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial		0.008		n.a.	
Short term	24h	0.008	0.008	n.a.	n.a.
	2d	0.008	0.008	n.a.	n.a.
	4d	0.008	0.008	n.a.	n.a.
Long term	7d	0.008	0.008	n.a.	n.a.
	28d	0.008	0.008	n.a.	n.a.
	50d	0.007	0.008	n.a.	n.a.
	100d	0.006	0.007	n.a.	n.a.
Plateau concentration		0.0148 mg/kg after 10 year (= Steady state concentration 0.0068 mg/kg + annual soil loading 0.008 mg/kg) Based on application of 6 g a.s./ha, evenly distributed over 5 cm soil depth (bulk density of 1.5 g/cm^3) and assuming a 'pseudo' 1st order DT_{50} of 325.3 d.			

M01

Method of calculation	Molecular weight relative to the parent: 231.6/ 247.7 g/mol = correction factor of x 0.932 DT_{50} (d): 56.7 days Kinetics: SFO Field or Lab: worst-case laboratory DT_{50} (3/4 soils with acceptable fit), calculated from peak amount with non-linear regression analysis.
Application data	Application rate assumed: 6 g a.s./ha corrected for molecular weight is 5.592 g/ha, then corrected to 0.989784 g /ha assuming M01 is formed at a maximum of 17.7 % of the applied dose.

PEC$_{(s)}$ (mg/kg)		Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial		0.00132		n.a.	
Short term	24h	0.001304	0.001311	n.a.	n.a.
	2d	0.001288	0.001304	n.a.	n.a.
	4d	0.001256	0.001288	n.a.	n.a.
Long term	7d			n.a.	n.a.
	28d	0.000938	0.001117	n.a.	n.a.
	50d	0.000716	0.000987	n.a.	n.a.
	100d	0.000389	0.000761	n.a.	n.a.
Plateau concentration		Not required as DT_{90} values for M01 <1 year. Therefore, a maximum PEC_{soil} of M01 formed from the accumulated parent residues has been calculated. i.e. 17.7 % x 0.932 of 0.0148 mg/kg = 0.002441 mg/kg.			

M02	
Method of calculation	Molecular weight relative to the parent: 231.6/196.6g/mol = correction factor of x 0.794 DT_{50} (d): 313 days Kinetics: SFO Field or Lab: Worst-case DT_{50} from non-normalised field data (decline from maximum observed).
Application data	Application rate assumed: 6 g a.s./ha corrected for molecular weight is 4.762 g/ha, then corrected to 0.8905 g /ha assuming M02 is formed at a maximum of 18.7 % of the applied dose.

PEC$_{(s)}$ (mg/kg)		Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial		0.001187		n.a.	
Short term	24h	0.001185	0.001186	n.a.	n.a.
	2d	0.001182	0.001185	n.a.	n.a.
	4d	0.001169	0.001182	n.a.	n.a.
Long term	7d	0.001169	0.001178	n.a.	n.a.
	28d	0.001116	0.001152	n.a.	n.a.
	50d	0.001063	0.001124	n.a.	n.a.
	100d	0.000952	0.001065	n.a.	n.a.
Plateau concentration		0.002141 mg/kg (= Steady state concentration 0.000954 mg/kg + annual soil loading 0.001187 mg/kg).			

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

Hydrolytic degradation of the active substance and metabolites > 10 % ‡	pH 4: hydrolytically stable at 20 °C (extrapolated from study performed at 50 °C). No metabolites >10 % AR
	pH 7: DT_{50} = 745 d at 20°C (extrapolated 'pseudo1st order'). DT_{50} = 495 d at 25ºC, r^2 = 0.6427 (poor correlation attributed to slope of regression line approaching zero). Both estimates beyond study duration. No metabolites >10 % AR
	pH 9: DT_{50} = 6.9 d at 20°C (extrapolated pseudo1st order). DT_{50} = 6.6 d at 25ºC, r^2 = 0.997 M04: max. 97.3 % AR (30 d, 25°C)
Photolytic degradation of active substance and metabolites above 10 % ‡	DT_{50} : 24.4 experimental hours Natural light: Equated to 3.5 solar days at Phoenix, Arizona, USA (33º30'N). (Not equated to 40ºN). M05: max. 49.2 % AR (60 hours, study end).
Quantum yield of direct phototransformation in water at ☒ > 290 nm	Triazoxide: $\Phi = 2 \times 10^{-5}$ M05: $\Phi = 9.725 \times 10^{-5}$
Readily biodegradable ‡ (yes/no)	No data submitted; substance considered not ready biodegradable.

Degradation in water / sediment

Parent	Distribution (max. in water 36.5 % AR after 0 d ('Lienden'). Max. sed 22.8 % AR after 0 d ('Lienden')).									
Water / sediment system	pH water phase	pH sed	t °C	DT_{50}-DT_{90} whole sys. (days)	St. (r^2)	DT_{50}-DT_{90} Water (days)	St. (r^2)	DT_{50}-DT_{90} sed	St. (r^2)	Method of calculation
Ijzendoorn	7.68-8.48	n.r.	22±2	*	0.498	*	0.498	n.c.		SFO Excel Solver
Lienden	7.98-8.91	n.r.	22±2	4.3 /14.2	0.866	*	0.866	n.c.		
Geometric mean/median				n.a.		n.a.				

* Values calculated but found to be unreliable due to the rapid degradation or dissipation of the substance and the timing of the samples (0 and 15 d).
n.a. not applicable.

M01	Distribution (max in water 6.2 % AR after 91d ('Lienden'). Max. sed 47.4 % AR after 30 d ('Ijzeendoorn'))									
Water / sediment system	pH water phase	pH sed	t. °C	DT_{50}-DT_{90} whole sys. (days)	St. (r^2)	DT_{50}-DT_{90} water (days)	r^2	DT_{50}-DT_{90} sed	St. (r^2)	Method of calculation
Ijzendoorn	7.68-8.48	n.r.	22±2	DT_{50}: *	0.498	n.c.		n.c.		SFO Excel

Lienden	7.98-8.91	n.r.	22±2	DT_{50}: 323	0.866	n.c.		n.c.		Solver
Geometric mean/median			22±2	n.a.		n.c.		n.c.		
M05	Distribution in water: max. 3.5 % AR after 0 d ('Lienden' system). Distribution in sediment: max. 9.8 % after 60 days ('Lienden' system, TLC analysis, 13.4 % AR after 30 days, 'Lienden' system, HPLC analysis). * Available data considered not reliable for exposure assessment.									

Mineralization and non extractable residues

Water / sediment system	pH water phase	pH sed	Mineralization x % after n d. (end of the study).	Non-extractable residues in sed. max x % after n d	Non-extractable residues in sed. max x % after n d (end of the study)
Ijzendoorn	7.68-8.48	n.r.	0.3 % after 91 d	55.7% after 91 d	55.7 % after 91 d
Lienden	7.98-8.91	n.r.	0.9 % after 91 d	36.2% after 30 d	35.5 after 91 d

n.c. – not calculated n.r. – not reported * Value found unreliable, not to be used for risk assessment

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

Parent Parameters used in FOCUSsw step 1 and 2	Version control no. of FOCUS calculator: v.1.1 Molecular weight (g/mol): 247.7 Water solubility (mg/L): 34 K_{OC}/K_{OM} (L/kg): 673 DT_{50} water/sediment system (d): 4.3 days (representative worst case from sediment water studies) DT_{50} water (d): 4.3 days (whole system) DT_{50} sediment (d): 4.3 days (whole system) Crop interception (%): none, seed treatment. PECsw and PECsed were calculated for parent with field DT_{50} soil of 110 (geometric mean, slow phase, field study)
Parameters used in FOCUSsw step 3 (if performed)	Version control no.'s of FOCUS software: v1.1 Vapour pressure: 1.0 x 10^{-7} Pa at 20°C K_{Foc}: 673 mL/g 1/n: 0.771 DT_{50} soil (d): 110 (geometric mean, slow phase, field study) 5.75*† Q10=2.58, Walker coefficient 0.7.
Application rate	Crop: winter cereal seed treatment Crop interception: none, seed treatment Number of applications: 1 Application rate(s): 6 g a.s./ha Application window: October - February

*The slow phase DT_{50} was used as a conservative assessment for the parent compound. To ensure that a conservative assessment of potential metabolite leaching was performed additional modelling was carried out using DT_{50} values calculated from the fast phase of degradation.
†The value of 3.63 d is considered to be the appropriate fast phase parent DT_{50} for use in future modelling.

FOCUS STEP 1 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
	0 h	1.0541		7.0942	
	24 h	0.8972	0.9756	6.0380	6.5661
	2 d	0.7636	0.9021	5.1391	6.0713
	4 d	0.5532	0.7774	3.7228	5.2321
	7 d	0.3411	0.6322	2.2954	4.2548
	14 d	0.1104	0.4183	0.7427	2.8154
	21 d	0.0357	0.3009	0.2403	2.0254
	28 d	0.0116	0.2311	0.0778	1.5550
	42 d	0.0012	0.1556	0.0081	1.0470

FOCUS STEP 1 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
	50 d	0.0003	0.1308	0.0022	0.8802
	100 d	0.0000	0.0654	0.0000	0.4402

FOCUS STEP 2 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Northern EU	0 h	0.5139		3.4588	
	24 h	0.4374	0.4757	2.9439	9.2013
	2 d	0.3723	0.4403	2.5056	2.9630
	4 d	0.2697	0.3976	1.8151	2.5547
	7 d	0.1663	0.3088	1.1191	2.0780
	14 d	0.0538	0.2043	0.3621	1.3752
	21 d	0.0174	0.1470	0.1172	0.9893
	28 d	0.0056	0.1129	0.0379	0.7596
	42 d	0.0006	0.0760	0.0040	0.5114
Southern EU*	0 h	0.4111		2.7670	
	24 h	0.3499	0.3805	2.3551	2.5611
	2 d	0.2978	0.3522	2.0045	2.3704
	4 d	0.2158	0.3037	1.4521	2.0438
	7 d	0.1330	0.2470	0.8953	1.6624
	14 d	0.0430	0.1635	0.2897	1.1001
	21 d	0.0139	0.1176	0.0937	0.7914
	28 d	0.0045	0.0903	0.0303	0.6076
	42 d	0.0005	0.0608	0.0032	0.4091

*PECsw/sed values for triazoxide (southern EU) are for approach at DAR (B.8.6.a), i.e. geometric mean, normalised $DT50_{soil}$ of 305.4 days (2^{nd} dissipation phase), not recalculated for B.8.6.b. as DT_{50} more worst-case & higher northern EU values above were used for the risk assessment.

FOCUS Step 3

Scenario	Water body	PEC_{sw}[µg l^{-1}]		PEC_{sed} [µg kg^{-1} dry weight]	
		winter cereals	spring cereals	winter cereals	spring cereals
D1 (Lanna)	ditch	< 1 x 10^{-15}	< 1 x 10^{-15}	< 0.001	< 0.001
D1 (Lanna)	stream	< 1 x 10^{-15}	< 1 x 10^{-15}	< 0.001	< 0.001
D2 (Brimstone)	ditch	< 1 x 10^{-15}	-	< 0.001	-
D2 (Brimstone)	stream	9.7 x 10^{-10}	-	< 0.001	-
D3 (Vredepeel)	ditch	< 1 x 10^{-15}	< 1 x 10^{-15}	< 0.001	< 0.001
D4 (Skousbo)	pond	2.7 x 10^{-7}	5.1 x 10^{-7}	< 0.001	< 0.001

D4 (Skousbo)	stream	**5.3×10^{-6}**	**5.2×10^{-6}**	< 0.001	< 0.001
D5 (La Jailliere)	pond	1.4×10^{-7}	8.7×10^{-8}	< 0.001	< 0.001
D5 (La Jailliere)	stream	2.1×10^{-6}	1.1×10^{-6}	< 0.001	< 0.001
D6 (Thiva)	ditch	2.0×10^{-6}	-	< 0.001	-
R1 (Weiherbach)	pond	$< 1 \times 10^{-15}$	-	< 0.001	-
R1 (Weiherbach)	stream	$< 1 \times 10^{-15}$	-	< 0.001	-
R3 (Bologna)	stream	$< 1 \times 10^{-15}$	-	< 0.001	-
R4 (Roujan)	Stream	$< 1 \times 10^{-15}$	$<1 \times 10^{-15}$	< 0.001	< 0.001

Metabolite M01	Molecular weight: 231.6
Parameters used in FOCUSsw step 1 and 2	Water solubility (mg/L): 34 (assumed as for parent) Soil or water metabolite: Soil Koc (L/kg): 2924 DT_{50} soil (d): 56.7 days (Laboratory, worst-case decline rate from peak amount, using non-linear fitting in Excel spreadsheet with Solver) DT_{50} water/sediment system (d): 323 days (representative worst-case from sediment water studies) DT_{50} water (d): 323 days (whole system) DT_{50} sediment (d): 323 days (whole system) Crop interception (%): none, seed treatment Maximum occurrence observed (% molar basis with respect to the parent) : 48.5 % AR whole system (30 DAT, 'Ijzendoorn') Water: 6.2 % AR (91 DAT, 'Lienden') Sediment: 47.4 % AR (30 DAT, 'Ijzendoorn') Soil: 17.7 % relative to the parent in molar basis (field studies).
Parameters used in FOCUSsw step 3 (if performed)	Whilst step 3 calculations were included in the resubmission dossier they are not relied on as information on how formation fraction of the metabolite was handled in the simulations was not adequately reported.
Application rate	Crop: winter cereal seed treatment Number of applications: 1 Interval (d): n/a Application rate(s): 6 g a.s./ha Depth of water body: 30 cm Application window: October- February
Main routes of entry	Run-off + drainage. No spray drift assumed.

FOCUS STEP 1 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
	0h	0.676		1.9757	
	24h	0.674	0.0675	1.9714	1.9736
	2d	0.0673	0.0674	1.9672	1.9714
	4d	0.0670	0.0673	1.9588	1.9672
	7d	0.0666	0.0671	1.9462	1.9609
	14d	0.0656	0.0666	1.9172	1.9463
	21d	0.0646	0.0661	1.8886	1.9318
	28d	0.0636	0.0656	1.8605	1.9175
	42d	0.0617	0.0646	1.8054	1.8893

FOCUS STEP 2 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Northern EU Winter barley	0 h	0.0230		0.6721	
	24 h	0.0229	0.0230	0.6707	0.6714
	2 d	0.0229	0.0229	0.6692	0.6707
	4 d	0.0228	0.0229	0.06664	0.6692
	7 d	0.0226	0.0228	0.6621	0.6671
	14 d	0.0223	0.0226	0.6522	0.6621
	21 d	0.0220	0.0225	0.6425	0.6572
	28 d	0.0216	0.0223	0.6329	0.6523
	42 d	0.0210	0.0220	0.6142	0.6427
Southern EU Winter barley	0 h	0.0184		0.5377	
	24 h	0.0183	0.0184	0.5365	0.5371
	2 d	0.0183	0.0183	0.5354	0.5365
	4 d	0.0182	0.0183	0.5331	0.5354
	7 d	0.0181	0.0183	0.5297	0.5337
	14 d	0.0178	0.0181	0.5218	0.5297
	21 d	0.0176	0.0180	0.5140	0.5258
	28 d	0.0173	0.0178	0.5063	0.5219
	42 d	0.0168	0.0176	0.4914	0.5142
FOCUS STEP 2 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Northern EU	0 h	0.0092		0.2688	

FOCUS STEP 2 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Spring Barley	24 h	0.0092	0.0092	0.2683	0.2686
	2 d	0.0092	0.0092	0.2677	0.2683
	4 d	0.0091	0.0092	0.2665	0.2677
	7 d	0.0091	0.0091	0.2648	0.2668
	14 d	0.0089	0.0091	0.2609	0.2648
	21 d	0.0088	0.0090	0.2570	0.2629
	28 d	0.0087	0.0089	0.2532	0.2609
	42 d	0.0084	0.0088	0.2457	0.2571
Southern EU Spring Barley	0 h	0.0184		0.5377	
	24 h	0.0183	0.0184	0.5365	0.5371
	2 d	0.0183	0.0183	0.5354	0.5365
	4 d	0.0182	0.0183	0.5331	0.5354
	7 d	0.0181	0.0183	0.5297	0.5337
	14 d	0.0178	0.0181	0.5218	0.5297
	21 d	0.0176	0.0180	0.5140	0.5258
	28 d	0.0173	0.0178	0.5063	0.5219
	42 d	0.0168	0.0176	0.4914	0.5142

Metabolite M02

Parameters used in FOCUSsw step 1 and 2

Molecular weight: 196.6

Water solubility (mg/L): 34 (assumed as for parent)

Soil or water metabolite: Soil

Koc (L/kg): 979

DT_{50} soil (d): 72 (Normalised Field DT_{50}, (Q10 2.58) geometric mean. In accordance with FOCUS SFO)

DT_{50} water/sediment system (d): M02 not detected.

DT_{50} water (d): 999 (default)

DT_{50} sediment (d): 999 (default)

Crop interception (%): none, seed treatment

Maximum occurrence observed (% molar basis with respect to the parent): not detected in water/sediment system.

Soil: 19.3 % AR (normalised mean amount field data. Max. 18.7 % (non-normalised field data).

Parameters used in FOCUSsw step 3 (if performed)	Vapour pressure: 1.0 x 10^{-7} K_{Foc}: 979 mL/g 1/n: 0.768 (Freundlich exponent for soil) Metabolite kinetically generated in simulation (yes): kinetic formation fraction from triazoxide 0.324 in soil. The substance was not formed in the sediment water experiments. Q10=2.58, Walker coefficient 0.7.
Application rate	Crop: winter cereal seed treatment Number of applications: 1 Interval (d): n/a Application rate(s): 6 g a.s./ha Depth of water body: 30 cm Application window: October- February
Main routes of entry	Run-off + drainage. No spray drift assumed.

FOCUS STEP 1 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
	0h	0.1288		1.2606	
	24h	0.1287	0.1287	1.2597	1.2602
	2d	0.1286	0.1287	1.2589	1.2597
	4d	0.1284	0.1286	1.2571	1.2589
	7d	0.1281	0.1285	1.2545	1.2575
	14d	0.1275	0.1281	1.2484	1.2545
	21d	0.1269	0.1278	1.2424	1.2515
	28d	0.1263	0.1275	1.2363	1.2484
	42d	0.1251	0.1269	1.2244	1.2424

FOCUS STEP 2 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Northern EU Spring barley	0 h	0.0248		0.2426	
	24 h	0.0248	0.0248	0.2424	0.2425
	2 d	0.0247	0.0248	0.2423	0.2424
	4 d	0.0247	0.0247	0.2419	0.2423
	7 d	0.0247	0.0247	0.2414	0.2420
	14 d	0.0245	0.0247	0.2403	0.2414
	21 d	0.0244	0.0246	0.2391	0.2408
	28 d	0.0243	0.0245	0.2379	0.2403
	42 d	0.0241	0.0244	0.2356	0.2391

FOCUS STEP 2 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Southern EU Spring barley	0 h	0.0496		0.4852	
	24 h	0.0495	0.0495	0.4849	0.4850
	2 d	0.0495	0.0495	0.4845	0.4849
	4 d	0.0494	0.0495	0.4838	0.4845
	7 d	0.0493	0.0494	0.4828	0.4840
	14 d	0.0491	0.0493	0.4805	0.4828
	21 d	0.0488	0.0492	0.4782	0.4817
	28 d	0.0486	0.0491	0.4759	0.4805
	42 d	0.0481	0.0488	0.4713	0.4782
FOCUS STEP 2 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Northern EU winter barley	0 h	0.0620		0.6065	
	24 h	0.0619	0.0619	0.6061	0.6063
	2 d	0.0619	0.0619	0.6056	0.6061
	4 d	0.0618	0.0619	0.6048	0.6056
	7 d	0.0616	0.0618	0.6036	0.6050
	14 d	0.0614	0.0617	0.6006	0.6036
	21 d	0.0611	0.0615	0.5977	0.6021
	28 d	0.0608	0.0614	0.5948	0.6006
	42 d	0.0602	0.0611	0.5891	0.5977
Southern EU winter barley	0 h	0.0496		0.4852	
	24 h	0.0495	0.0495	0.4849	0.4850
	2 d	0.0495	0.0495	0.4845	0.4849
	4 d	0.0494	0.0495	0.4838	0.4845
	7 d	0.0493	0.0494	0.4828	0.4840
	14 d	0.0491	0.0493	0.4805	0.4828
	21 d	0.0488	0.0492	0.4782	0.4817
	28 d	0.0486	0.0491	0.4759	0.4805
	42 d	0.0481	0.0488	0.4713	0.4782

FOCUS STEP 3 Scenario	Water body	PECsw (µg/l) Spring	PECsw (µg/l) Winter
D1	Ditch	$< 1 \times 10^{-15}$	$< 1 \times 10^{-15}$
D1	Stream	$< 1 \times 10^{-15}$	$< 1 \times 10^{-15}$
D2	Ditch	-	$< 1 \times 10^{-15}$

D2	Stream	-	3.7×10^{-11}
D3	Ditch	$< 1 \times 10^{-15}$	$< 1 \times 10^{-15}$
D4	Pond	3.3×10^{-8}	1.1×10^{-8}
D4	Stream	**2.4×10^{-7}**	**1.7×10^{-7}**
D5	Pond	5.3×10^{-9}	6.7×10^{-9}
D5	Stream	5.6×10^{-8}	6.4×10^{-8}
D6	Ditch	-	$< 1 \times 10^{-15}$
R1	Pond	-	$< 1 \times 10^{-15}$
R1	Stream	-	$< 1 \times 10^{-15}$
R3	Stream	-	$< 1 \times 10^{-15}$
R4	Stream	$< 1 \times 10^{-15}$	$< 1 \times 10^{-15}$

Metabolite M05	
Parameters used in FOCUSsw step 1 and 2	Molecular weight: 180.6 Water solubility (mg/L): 34 (assumed as for parent) Soil or water metabolite: Water (major in aqueous photolysis study, minor in hydrolysis study, present in water/sediment systems) Koc (L/kg): 979 (no data, as for M02) DT_{50} soil (d): 999 days (default) DT_{50} water/sediment system (d): not possible to determine DT_{50} water (d): 999 (default) DT_{50} sediment (d): 999 (default) Crop interception (%): none, seed treatment Maximum occurrence observed (% molar basis with respect to the parent) : 11.3 % AR whole system (60 DAT, 'Lienden') Individually: Water: 3.5% AR (0 DAT, 'Lienden') Sediment: 9.8 % AR (60 DAT, 'Lienden')
Parameters used in FOCUSsw step 3 (if performed)	Whilst step 3 calculations were included in the resubmission dossier they are not relied on as information on how formation fraction of the metabolite was handled in the simulations was not adequately reported.
Application rate	Crop: winter cereal seed treatment Number of applications: 1 Interval (d): n/a Application rate(s): 6 g a.s./ha Depth of water body: 30 cm Application window: October- February
Main routes of entry	Run-off + drainage. No spray drift assumed.

FOCUS STEP 1 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
	0h	0.0006		0.0062	
	24h	0.0006	0.0006	0.0062	0.0062
	2d	0.0006	0.0006	0.0062	0.0062
	4d	0.0006	0.0006	0.0062	0.0062
	7d	0.0006	0.0006	0.0062	0.0062
	14d	0.0006	0.0006	0.0061	0.0062
	21d	0.0006	0.0006	0.0061	0.0061
	28d	0.0006	0.0006	0.0061	0.0061
	42d	0.0006	0.0006	0.0060	0.0061

FOCUS STEP 2 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Northern EU Spring barley	0 h	<0.0001		0.0003	
	24 h	<0.0001	<0.0001	0.0003	0.0003
	2 d	<0.0001	<0.0001	0.0003	0.0003
	4 d	<0.0001	<0.0001	0.0003	0.0003
	7 d	<0.0001	<0.0001	0.0003	0.0003
	14 d	<0.0001	<0.0001	0.0003	0.0003
	21 d	<0.0001	<0.0001	0.0003	0.0003
	28 d	<0.0001	<0.0001	0.0003	0.0003
	42 d	<0.0001	<0.0001	0.0003	0.0003
Southern EU Spring barley	0 h	<0.0001		0.0002	
	24 h	<0.0001	<0.0001	0.0002	0.0002
	2 d	<0.0001	<0.0001	0.0002	0.0002
	4 d	<0.0001	<0.0001	0.0002	0.0002
	7 d	<0.0001	<0.0001	0.0002	0.0002
	14 d	<0.0001	<0.0001	0.0002	0.0002
	21 d	<0.0001	<0.0001	0.0002	0.0002
	28 d	<0.0001	<0.0001	0.0002	0.0002
	42 d	<0.0001	<0.0001	0.0002	0.0002

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

Method of calculation and type of study (*e.g.* modelling, field leaching, lysimeter)	For FOCUS gw modelling, values used – Modelling using FOCUS model(s), with appropriate FOCUSgw scenarios, according to FOCUS guidance. Model used: FOCUS PEARL 3.3.3, FOCUS PELMO 3.3.2, FOCUS MACRO 4.4.2 Scenarios (list of names): All 9 FOCUS scenarios for winter cereals. Plus Châteaudun, Hamburg, Jokioinen, Kremsmünster, Okehampton and Porto scenarios for spring cereals. Incorporation depth: 2.5 cm **Parent**: Geometric mean parent $DT_{50field}$: 110 d (slow phase), 5.75 d† (fast phase) (normalisation to pF2, 20°C with Q10 of 2.58)*. K_{OC}: parent, arithmetic mean, 673 mg/l, $^1/_n$= 0.771. **Metabolites:** **M01:** Geometric mean parent DT_{50} lab 7.2 d (normalisation to 10kPa or pF2, studies were at 20°C). K_{OC}: arithmetic mean, 2924 mg/l, $^1/_n$= 0.734. Formation fraction: 0.177 (maximum occurrence (observed, not kinetically derived) in field studies). **M02:** K_{OC}: arithmetic mean, 979 mg/l, $^1/_n$= 0.768. Geometric mean parent DT_{50} field normalised 72 d (normalisation to pF2, 20 ºC with Q10 of 2.58) Formation fraction: 0.324 (worst-case kinetically derived from field studies) No field leaching or lysimeter studies submitted.
Application rate	Application rate: 6 g a.s./ha. No. of applications: 1 Time of application (month or season): Sept – Nov; Feb – May

*The slow phase DT_{50} was used as a conservative assessment for the parent compound. To ensure that a conservative assessment of potential metabolite leaching was performed, additional modelling was carried out using DT_{50} values calculated from the fast phase of degradation.

†The value of 3.63 d is considered to be the appropriate fast phase parent DT_{50} for use in future modelling.

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

PEARL Spring barley Slow DT_{50}	Scenario	Parent (µg/L)	Metabolite (µg/L)	
			M01	M02
	Chateaudun	<0.0001	<0.0001	<0.0001
	Hamburg	<0.0001	<0.0001	<0.0001
	Jokioinen	<0.0001	<0.0001	<0.0001
	Kremsmunster	<0.0001	<0.0001	<0.0001
	Okehampton	<0.0001	<0.0001	<0.0001
	Porto	<0.0001	<0.0001	<0.0001
PEARL Winter barley Slow DT_{50}	Chateaudun	<0.0001	<0.0001	<0.0001
	Hamburg	<0.0001	<0.0001	<0.0001
	Jokioinen	<0.0001	<0.0001	<0.0001
	Kremsmunster	<0.0001	<0.0001	<0.0001
	Okehampton	<0.0001	<0.0001	<0.0001
	Porto	<0.0001	<0.0001	<0.0001
	Piacenza	<0.0001	<0.0001	<0.0001
	Sevilla	<0.0001	<0.0001	<0.0001
	Thiva	<0.0001	<0.0001	<0.0001

PEARL Spring barley Fast DT_{50}	Scenario	Parent (µg/L)	Metabolite (µg/L)	
			M01	M02
	Chateaudun	<0.0001	<0.0001	<0.0001
	Hamburg	<0.000	<0.0001	<0.0001
	Jokioinen	<0.0001	<0.0001	<0.0001
	Kremsmunster	<0.0001	<0.0001	<0.0001
	Okehampton	<0.0001	<0.0001	<0.0001
	Porto	<0.0001	<0.0001	<0.0001
PEARL Winter barley Fast DT_{50}	Chateaudun	<0.0001	<0.0001	<0.0001
	Hamburg	<0.0001	<0.0001	<0.0001
	Jokioinen	<0.0001	<0.0001	<0.0001
	Kremsmunster	<0.0001	<0.0001	<0.0001
	Okehampton	<0.0001	<0.0001	<0.0001
	Porto	<0.0001	<0.0001	<0.0001
	Piacenza	<0.0001	<0.0001	<0.0001
	Sevilla	<0.0001	<0.0001	<0.0001
	Thiva	<0.0001	<0.0001	<0.0001

PELMO Spring barley Slow DT_{50}	Scenario	Parent (µg/L)	Metabolite (µg/L)	
			M01	M02
	Chateaudun	<0.0001	<0.0001	<0.0001
	Hamburg	<0.0001	<0.0001	<0.0001
	Jokioinen	<0.0001	<0.0001	<0.0001
	Kremsmunster	<0.0001	<0.0001	<0.0001
	Okehampton	<0.0001	<0.0001	<0.0001
	Porto	<0.0001	<0.0001	<0.0001
PELMO Winter barley Slow DT_{50}	Chateaudun	<0.0001	<0.0001	<0.0001
	Hamburg	<0.0001	<0.0001	<0.0001
	Jokioinen	<0.0001	<0.0001	<0.0001
	Kremsmunster	<0.0001	<0.0001	<0.0001
	Okehampton	<0.0001	<0.0001	<0.0001
	Porto	<0.0001	<0.0001	<0.0001
	Piacenza	<0.0001	<0.0001	<0.0001
	Sevilla	<0.0001	<0.0001	<0.0001
	Thiva	<0.0001	<0.0001	<0.0001

PELMO Spring barley Fast DT_{50}	Scenario	Parent (µg/L)	Metabolite (µg/L)	
			M01	M02
	Chateaudun	<0.0001	<0.0001	<0.0001
	Hamburg	<0.0001	<0.0001	<0.0001
	Jokioinen	<0.0001	<0.0001	<0.0001
	Kremsmunster	<0.0001	<0.0001	<0.0001
	Okehampton	<0.0001	<0.0001	<0.0001
	Porto	<0.0001	<0.0001	<0.0001
PELMO Winter barley Fast DT_{50}	Chateaudun	<0.0001	<0.0001	<0.0001
	Hamburg	<0.0001	<0.0001	<0.0001
	Jokioinen	<0.0001	<0.0001	<0.0001
	Kremsmunster	<0.0001	<0.0001	<0.0001
	Okehampton	<0.0001	<0.0001	<0.0001
	Porto	<0.0001	<0.0001	<0.0001
	Piacenza	<0.0001	<0.0001	<0.0001
	Sevilla	<0.0001	<0.0001	<0.0001
	Thiva	<0.0001	<0.0001	<0.0001

MACRO Winter barley Slow DT_{50}	Scenario	Parent (µg/L)	Metabolite (µg/L)	
			M01	M02
	Chateaudun	<0.0001	<0.0001	<0.0001
MACRO Spring barley Slow DT_{50}	Scenario	Parent (µg/L)	Metabolite (µg/L)	
			M01	M02
	Chateaudun	<0.0001	<0.0001	<0.0001

MACRO Winter barley	Scenario	Parent (µg/L)	Metabolite (µg/L)	
			M01	M02

Fast DT_{50}	Chateaudun	<0.0001	<0.0001	<0.0001
MACRO Spring barley Fast DT_{50}	Scenario	Parent (µg/L)	Metabolite (µg/L)	
			M01	M02
	Chateaudun	<0.0001	<0.0001	<0.0001

$PEC_{(gw)}$ From lysimeter / field studies

Parent	1st year	2nd year	3rd year
Annual average (µg/L)	NOT PERFORMED	NOT PERFORMED	NOT PERFORMED

Metabolite X	1st year	2nd year	3rd year
Annual average (µg/L)	NOT PERFORMED	NOT PERFORMED	NOT PERFORMED

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

Direct photolysis in air ‡	Not studied - no data requested.
Quantum yield of direct phototransformation in water	Triazoxide: $\Phi = 2 \times 10^{-5}$ Triazoxide-desoxyamino (M05): $\Phi = 9.725 \times 10^{-5}$
Photochemical oxidative degradation in air ‡	DT_{50} of 10.5 hours derived by the Atkinson model (version 1988, AOPWIN v 1.90). OH (24 h) concentration assumed = 0.5×10^6 radicals/cm^3
Volatilisation ‡	from plant surfaces: No data submitted, not required.
	from soil surfaces: No data submitted, not required.
Metabolites	No information submitted on the volatility of the metabolites.

PEC (air)

Method of calculation	Expert judgement, based on vapour pressure, dimensionless Henry's Law Constant and method of application of product.

$PEC_{(a)}$

Maximum concentration	negligible

Residues requiring further assessment

Environmental occurring metabolite requiring further assessment by other disciplines (toxicology and ecotoxicology) or for which a groundwater exposure assessment is triggered.	Soil: triazoxide, M01, M02 Surface water: triazoxide Sediment: triazoxide, M01, M02, M05 Ground water: triazoxide, M01, M02 Air: triazoxide

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

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

Candidate for R53

Ecotoxicology

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

Species	Test substance	Time scale	End point (mg/kg bw/(day))	End point (mg/kg feed)
Birds				
Japanese quail *Coturnix coturnix japonica*	a.s.	Acute	90	
Mallard duck *Anas platyrhyncus*	a.s.	Short-term	Approximately 268.1[1]	849.5
Japanese quail *Coturnix japonica*	a.s.	Long-term (6-week study)	11.7	100
Mammals				
Rat	a.s.	Acute	98	
Rat	a.s.	Long-term	2.04	25 ppm
Additional higher tier studies				
Residues decline study (Barknecht 2002b, presented in the DAR, Vol3 B.9.1.6) measured dissipation of triazoxide from treated barley seed placed onto soil surface giving a 10-day ftwa of 0.46. Higher tier ecological data have been submitted that indicated that wood pigeon, yellowhammer, skylark and chaffinch are potential focal species. PT values of 1.0, 0.22, 0.35 and 1.00 have been used for the skylark, chaffinch, yellowhammer and wood pigeon, respectively. PD values of 0.42, 0.32, 0.58 and 1.00 have been used for the skylark, chaffinch, yellowhammer and wood pigeon, respectively. As regards the risk to small mammals, again residue decline data have been used to revise the risk assessment. Further ecological data have been submitted that indicated that PD could be set to 0.66. Data on PT were submitted, however due to uncertainties regarding the number of individuals tracked and the population surveyed, it was not used to quantitatively refine the risk assessment. Data on de-husking as well as palatability of treated seed were not considered to be appropriate to quantitatively refine the risk assessment.				

[1] based on consumption in group where 30 % mortality was reported, as dose-response relationship was uncertain at higher exposure levels due to food avoidance.

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

Use as a seed treatment on barley at a dose equivalent of 1.5 µg triazoxide/seed, drilling rate 6 g a.s./ha (sowing rate 200 kg seed/ha)

Indicator species/Category[2]	Time scale	ETE	TER	Annex VI Trigger
Tier 1 (Birds)				
Granivorous	Acute	11.4	**7.9**[1]	10
Granivorous	Short-term	11.4	23.5	10
Granivorous	Long-term	11.4	**1**[2] **2.23** [1a] **2.6** [1b] 7.1 [1c]	5
Higher tier refinement (Birds)				
	Acute	9.9[3]	**9.1**[4]	10
	Long-term	11.4	**6.4 – 35.5** See box below for details	5
Tier 1 (Mammals)				
Granivorous	Acute	6.9	14.2	10
Granivorous	Long-term	6.9	**0.3**	5
Higher tier refinement (Mammals)				
	Long-term	3.17	**0.97**	5

Higher tier ecological data have been submitted that indicate that wood pigeon, yellowhammer, skylark and chaffinch are potential focal species. PT values of 1.0, 0.22, 0.35 and 1.00 have been used for the skylark, chaffinch, yellowhammer and wood pigeon respectively. PD values of 0.42, 0.32, 0.58 and 1.00 have been used for the skylark, chaffinch, yellowhammer and wood pigeon, respectively.

On the basis of the refinements proposed, it is concluded that the long-term/reproductive risk from the use of triazoxide treated seed for the spring use is low; TERlt for the skylark, chaffinch, yellowhammer and wood pigeon of 7.0, 35.5, 13 and 6.4 were determined. The risk from the use on autumn sown seed is also considered to be low on the basis of the lack of breeding at that time of year for northern Member States.

As regards the risk to small mammals, again residue decline data have been used to revise the risk assessment. Additional ecological data have been submitted that indicated that PD could be set to 0.66. Data on PT were submitted, however due to uncertainties regarding the number of individuals tracked and the population surveyed, they were not used to quantitatively refine the risk assessment. Data on de-husking as well as palatability of treated seed were not considered to be appropriate to quantitatively refine the risk assessment. As a result of the above refinements, the TERlt was 0.97.

[1] based on SANCO 4145 (European Commission, 2002a) first-tier assumption for a small generic 15 g bird

1[a] on basis of a refined f_{twa} of 0.46 .

1[b] based on the use of yellowhammer as focal species.

1[c] based on the use of woodpigeon as focal species.

[2] relevant for the spring use for which further refinement is required. Autumn/winter use considered to be outside of main reproductive period for northern Member States.

[3] based of an FIR/bw of 0.33 (based on SANCO values: DEE 98.2 kJ/d (Passeriformes), Energy content of food (16.7 kJ/g diet), Moisture content of food 13.3%). All other assumptions remain as first tier SANCO 4145 (European Commission, 2002a) values.

[4] Small focal species yellowhammer: Number of seeds required for median LD_{50} dose 159 (including a 10-fold uncertainty factor). Based on an incorporation efficiency of 90 % this requires the consumption of all surface seeds over an area of 3.45 m^2 in an acute timescale. Actual risk is considered to lie between acute and dietary TERs. Acute/dietary risk to relevant small granivorous focal species is considered to be low. Fast-feeding medium-sized birds are unlikely to consume sufficient seeds for LD_{50} dose. The number of seeds required for an LD_{50} dose for a medium-sized bird (490 g woodpigeon) is 2940 (this includes a 10-fold uncertainty factor).

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				
Bluegill sunfish *Lepomis macrochirus*	a.s.	96 hr (static)	Mortality, EC_{50}	0.077 $_{nom}$
No chronic study presented[2]	a.s.	28 d (static)	Growth NOEC	NA
No formulation study presented	Preparation	96 hr (flow-through)	Mortality, EC_{50}	NA
No metabolite studies presented	Metabolites	96 hr (flow-through)	Mortality, EC_{50}	NA
Aquatic invertebrate				
Daphnia magna	a.s.	48 h (static)	Mortality, EC_{50}	7.2 $_{nom}$
No chronic study presented[2]	a.s.	21 d (static)	Reproduction, NOEC	NA
No formulation study presented	Preparation	48 h (static)	Mortality, EC_{50}	NA
No metabolite studies presented	Metabolites	48 h (static)	Mortality, EC_{50}	NA
Sediment dwelling organisms				
No active substance study presented	a.s.	28 d (static)	NOEC	NA
Chironomus riparius	Metabolite M01	28 d (static) spiked sediment study	NOEC	10 mg/kg sed $_{nom}$
Algae				
Pseudokirchneriella subcapitata	a.s.	72 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	0.039 mm 0.074 mm
No formulation study presented	Preparation	72 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	NA
No metabolite studies presented	Metabolites	72 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	NA

Group	Test substance	Time-scale (Test type)	End point	Toxicity[1] (mg/L)
Higher plant				
No study presented or required				
Microcosm or mesocosm tests				
No additional higher tier studies presented or required				

[1] Presented as nominal ($_{nom}$) or mean measured concentrations ($_{mm}$).

[2] No chronic toxicity data have been presented for fish or aquatic invertebrates. Given the small margin of safety from the acute test and no information about long-term exposure, the PRAPeR 48 meeting of experts concluded that an additional chronic study was needed for fish. However, during the resubmission procedure it was considered that a chronic study is no longer necessary, as the chronic risk was considered to be low based on the very low exposure observed at step 3 presented in the Additional Report.

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

Crop and application rate: Barley seed treatment at rate equivalent to 6 g a.s./ha.

Test substance	Organism	Toxicity end point (mg/L)	Time scale	PEC_i (mg/l)[1]	TER	Annex VI Trigger
Step 1						
a.s.	Fish	0.077	Acute	0.001	**77**	100
a.s.	Aquatic invertebrates	7.2	Acute	0.001	7200	100
a.s.	Algae	E_bC_{50} 0.039 E_rC_{50} 0.074	Chronic	0.001	39 74	10
Step 2						
a.s.	Fish	0.077	Acute	0.0005	154	100
Step 1						
M01	Fish	0.0077*	Acute	0.00007	111.4	100
M01	Aquatic invertebrates	0.72*	Acute	0.00007	10285	100
M01	Algae	0.0039*	Chronic	0.00007	55	10
M01	*Chironomus riparius*	NOEC 10 mg/kg	Chronic	0.0020 mg/kg sed	5000	10
Step 1						
M02	Fish	0.0077*	Acute	0.00013	**60**	100
M02	Aquatic invertebrates	0.72*	Acute	0.00013	5538	100
M02	Algae	0.0039*	Chronic	0.00013	30	10
Step 2						
M02	Fish	0.0077*	Acute	0.00006	128	100

Test substance	Organism	Toxicity end point (mg/L)	Time scale	PEC_i (mg/l)[1]	TER	Annex VI Trigger
Step 1						
M05	Fish	0.0077*	Acute	0.0000006	12833	100
M05	Aquatic invertebrates	0.72*	Acute	0.0000006	1200000	100
M05	Algae	0.0039*	Chronic	0.0000006	6500	10

1 PEC values represent worst-case values for winter barley in northern EU

* Toxicity endpoints are based on the assumption that the metabolites are 10 times more toxic than the parent.

Bioconcentration			
	Active substance	Metabolite M01	Metabolite M02
$logP_{OW}$[1]	2.04	0.92	Not available

[1] log $P_{O/W}$ <3 for parent triazoxide and metabolite M01, therefore no assessment required. No definitive log Po/w value presented for M02 but unlikely to be >3.0.

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)
Technical triazoxide	>225	>200
Preparation	None presented, not required	
Metabolites	None presented, not required	
Field or semi-field tests	None presented, not required	

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

For the representative use as a seed treatment standard hazard quotients are not considered appropriate. Given the low toxicity and low systemicity of the substance the risk to bees is considered to be low.

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

Laboratory tests with standard sensitive species

No data with the technical active substance presented

Species	Test Substance	End point	Effect (LR_{50} g/ha[1])
Typhlodromus pyri	'Triazoxide FS 050'	Mortality + Reproduction	>5.7 g a.s./ha
Aphidius rhopalosiphi	'Triazoxide FS 050'	Mortality + Reproduction	>5.13 g a.s./ha

[1] LR_{50} values could not be calculated due to low incidence of effects reported at the highest dose tested.

Further laboratory and extended laboratory studies

Species	Life stage	Test substance, substrate and duration	Dose (g/ha)	End point	% effect	Trigger value
Poecilus cupreus	Adults	'Raxil S FS 040' – treated seeds ext. laboratory, natural soil, 14 d	190 kg seeds/ha	Mortality Feeding capacity	0 [1] +13[2]	50 %[3]
Pardosa spp.	Adults	'Raxil S FS 040' – treated seeds ext. laboratory, Lufa 2.1 soil, 14 d	245 kg seeds/ha	Mortality Feeding capacity	+ 9.4 [1] -23 [2]	50 %[3]
Aleochara bilineata	Young Adults	'Raxil S FS 040' – treated seeds ext. laboratory, Lufa 2.1 sand, 78 d	215 kg seeds/ha	Mortality Reproduction	Mortality of adults not reported +20 % [2]	50 %[3]

[1] corrected for mortality in the control

[2] effect relative to control, a positive percentage indicates an adverse effect, a negative percentage indicates a lack of adverse effect

[3] Due to the use being a seed treatment a standard ESCORT 2 risk assessment was not conducted. The 50 % trigger for ESCORT 2 and Annex VI is therefore applied.

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 fetida	Technical triazoxide	Acute 14 days	LC_{50} >500$_{corr}$ mg a.s./kg d.w.soil[1]
Eisenia fetida	'Raxil S FS 040' mixed into test soil	Acute	14 d LC_{50} >1000 mg 'Raxil S FS 040'/kg d.w soil (>20 mg triazoxide)[5]
Eisenia fetida	Metabolite M01	Acute	LC_{50} >1000 mg /kg d.w. soil
Eisenia fetida	Metabolite M02	Acute	LC_{50} >500$_{corr}$ mg /kg d.w.soil[1]
Eisenia fetida	'Raxil S FS 040' as treated seed	Chronic	NOEC 950 kg treated seed/ha
Eisenia fetida	'Triazoxide FS 050' mixed into soil	Chronic	56 d NOEC 15.1 mg /kg d.w. soil
Eisenia fetida	Metabolite M01 (97% w/w)	Chronic	56 d NOEC 10 mg /kg d.w. soil
Other soil macro-organisms			
Collembola			
Folsomia candida	Technical triazoxide mixed into OECD 207 artificial soil 28 d study	Chronic	$NOEC_{repro+mortality\ corr}$ 250 mg a.s./kg dw soil[1]
Folsomia candida	M01 mixed into OECD 207 artificial soil 28 d study	Chronic	LC_{50} >100[2] mg/kg d.w. soil NOEC 100 mg/kg d.w. soil

Test organism	Test substance	Time scale	End point[1]
Folsomia candida	'Raxil S FS 040' mixed into OECD 207 artificial soil 28 d study	Chronic	LC_{50} > 2500 mg 'Raxil S FS 040'/kg dw soil[3] NOEC 2500 mg 'Raxil S FS 040'/kg d.w. soil
Soil micro-organisms			
Nitrogen mineralisation	Technical triazoxide		No significant effect at day 28 at 0.038 mg a.s./kg d.w.soil
	Metabolite M01		No significant effect at day 28 at 0.036 mg M01/kg d.w.soil
	'Raxil S FS 040'		No significant effect at day 28 at 1.43 l product/ha
Carbon mineralisation	'Raxil S FS 040'		No significant effect at day 28 at 1.43 l product/ha
Litter bag study			
Based on a pre-EPFES 2002 protocol measured concentrations 7 days after spray were 3.70 µg triazoxide/kg soil (and 7.18 µg tebuconazole) based on soil depth of 10 cm. The annual rate was applied as treated seed at a rate equivalent to 4.21 g tebuconazole/ha and 3.81 g triazoxide/ha. No significant effect on degradation of straw at any evaluation time (28, 56, 84, and 184 DAA). Relevance of study not established. Therefore, new study submitted.			
Based on OECD: Guidance Document on the Breakdown of Organic Matter in Litter Bags, Paris 2006. Tebuconazole + triazoxide FS 20+20 g was tested at a plateau concentration of 6.8 µg/kg dry soil) plus seed treatment of annual application rate for triazoxide: 6 g/ha. Triazoxide as tested and at the rate of 6 g/ha had no influence on organic matter breakdown after 1, 3 and 6 months. A concentration of triazoxide of 0.00949 mg a.s./kg over 10 cm had no influence on organic matter breakdown after 1, 3 and 6 months.			

[1] toxicity end point has been corrected because log Pow >2.0 and the test substrate contained a high level of organic matter (10 %); the end point for metabolite M02 has been corrected as a precaution since it has not been established that the log Pow is <2.0.

[2] precise value not determined since only 2 data points available (26% mortality at 100 mg/kg soil, 78% mortality at 1000 mg/kg).

[3] precise value not determined since maximum mortality of 20% was reported at the highest dose tested.

Toxicity/exposure ratios for soil organisms

Test organism	Test substance	Time scale	Soil PEC[2]	TER	Trigger
Earthworms					
	triazoxide	Acute	0.015 mg triazoxide/kg d.w. soil[1]	>33333	10
	'Raxil S FS 040'	Acute	0.015 mg triazoxide/kg d.w. soil[1]	>1333	10
	Metabolite M01	Acute	0.00244 mg M01/kg d.w. soil[3]	>409836	10
	Metabolite M02	Acute	0.0021 mg M02/kg d.w. soil	>238096	5

Test organism	Test substance	Time scale	Soil PEC[2]	TER	Trigger
	'Raxil S FS 040' applied as treated seed using soil with 5% organic matter	Chronic	Max. proposed rate of use 200 kg treated seed/ha	**4.75**	5
	'Triazoxide FS 050' mixed into soil	Chronic	0.015 mg triazoxide[1]	1008	5
	Metabolite M01 (97 % w/w)	Chronic	0.00244 mg M01	4098	5
Other soil macro-organisms					
Collembola	Technical triazoxide	Chronic	0.015 mg triazoxide /kg d.w. soil	16666	5
	'Raxil S FS 040'	Chronic	0.015 mg triazoxide/kg d.w. soil	3333	5
	Metabolite M01	Chronic	0.00244 mg M01/kg d.w. soil	40984	5
Soil litter processes					
Based on OECD: Guidance Document on the Breakdown of Organic Matter in Litter Bags, Paris 2006. Tebuconazole + triazoxide FS 20+20 g was tested at a plateau concentration of 6.8 µg/kg dry soil) plus seed treatment of annual application rate for triazoxide: 6 g/ha. Triazoxide as tested and at the rate of 6 g/ha had no influence on organic matter breakdown after 1, 3 and 6 months. A concentration of triazoxide of 0.00949 mg a.s./kg over 10 cm had no influence on organic matter breakdown after 1, 3 and 6 months. It is also considered that this study addresses the risk from metabolites M01 and M02.					

[1] peak plateau concentration (steady state PECsoil accumulation + annual soil loading (Section B.8.3 of the AR (e))
[2] based on triazoxide content of 20 g /l product and an approximate specific density of 1 and the assumption that toxicity was due entirely to triazoxide. Study conducted using treated seed and does not address potential accumulation of triazoxide and soil metabolites M01 and M02.
[3] based on the amount that would be expected to be formed from the accumulated parent residue (rounded up from actual value of 0.00262 mg given in Section B.8.3 of the AR (d)).

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

Preliminary screening data

Not required as triazoxide is not a herbicide.

Laboratory dose response tests

In a pre-emergence study with the solo formulation 'Triazoxide FS 050' no visible signs of toxicity reported at up to 17.1 g a.s./ha in a total of 11 species. The representative use as a seed treatment effectively precludes exposure outside of the treated area, therefore a risk assessment currently not required under SANCO 10329 (European Commission, 2002c).

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

Test type/organism	end point
Activated sludge	EC_{50} >10000 mg technical triazoxide/l

Ecotoxicologically relevant compounds (to be confirmed)

Compartment	
soil	Triazoxide
water	Triazoxide
sediment	-
groundwater	Triazoxide

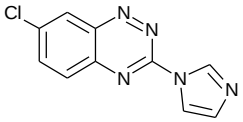
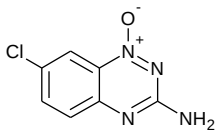
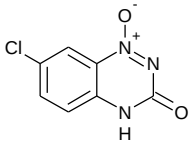
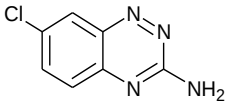
Classification and proposed labelling with regard to ecotoxicological data (Annex IIA, point 10 and Annex IIIA, point 12.3)

	RMS/peer review proposal
Active substance	R50 'Very toxic to aquatic organisms' R53 'May cause long term adverse effects in the aquatic environment' 'N' symbol

	RMS/peer review proposal[2]
Preparation Based on the calculation method [1]	R51 'Harmful to aquatic organisms' R53 'May cause long term adverse effects in the aquatic environment' 'N' symbol

[1] Member States should confirm this at product authorisation using agreed Annex I tebuconazole toxicity endpoints and/or formulation toxicity data for 'Raxil S FS 040'.
[2] based on Commission Directive 2006/8/EC (OJ L 19, 24.1.2006, p. 12)

APPENDIX B – USED COMPOUND CODE(S)

Code/Trivial name*	Chemical name**	Structural formula**
M01 desoxy-triazoxide	7-chloro-3-(1*H*-imidazol-1-yl)-1,2,4-benzotriazine	
M02 triazoxide-amino	7-chloro-1,2,4-benzotriazin-3-amine 1-oxide	
M04 triazoxide-oxone	7-chloro-1,2,4-benzotriazin-3(4*H*)-one 1-oxide	
M05 triazoxide-desoxyamino	7-chloro-1,2,4-benzotriazin-3-amine	

* The metabolite name in bold is the name used in the conclusion.
**ACD/ChemSketch, Advanced Chemistry Development, Inc., ACD/Labs Release: 12.00 Product version: 12.00 (Build 29305, 25 Nov 2008)

ABBREVIATIONS

1/n	slope of Freundlich isotherm
°C	degree Celsius (centigrade)
µg	microgram
µm	micrometer (micron)
ADI	acceptable daily intake
AOEL	acceptable operator exposure level
AR	applied radioactivity
ARfD	acute reference dose
a.s.	active substance
bw	body weight
CA	Chemical Abstract
CAS	Chemical Abstract Service
CF	conversion factor
CIPAC	Collaborative International Pesticide Analytical Council Limited
d	day
DAR	draft assessment report
DAT	days after treatment
DFOP	double first order in parallel kinetics
DM	dry matter
DNA	deoxyribonucleic acid
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
dt	deci tonne (ton)
d.w.	dry weight
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
ELS	early-life-stage
EMDI	estimated maximum daily intake
EPA	Environmental Protection Agency
ER_{50}	emergence rate, median
EU	European Union
FAO	Food and Agriculture Organisation of the United Nations
FC	field capacity
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
FOTC	first order two compartment
FS	flowable concentrate for seed treatment
GAP	good agricultural practice
GC-FPD	gas chromatography with flame photometric detector
GC-MSD	gas chromatography with mass-selective detection
GC-NPD	gas chromatography with nitrogen phosphorous detector
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
HPLC-DAD	high performance liquid chromatography with diode array detection
HPLC-MS/MS	high performance liquid chromatography with tandem mass spectrometry
HPLC-UV	high pressure liquid chromatography with ultraviolet detector

HR	highest residue
HQ	hazard quotient
HS	hockey stick kinetics
IE	immature erythrocytes
IEDI	international estimated daily intake
IESTI	international estimated short-term intake
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint Meeting on the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
KC+	kinetochore positive
K_{oc}	organic carbon adsorption coefficient
K_{doc}	organic carbon linear adsorption coefficient
kg	kilogram
K_{Foc}	Freundlich organic carbon adsorption coefficient
L	litre
LC	liquid chromatography
LC-MS	liquid chromatography-mass spectrometry
LC_{50}	lethal concentration, median
LD_{50}	lethal dose, median; dosis letalis media
LLNA	Local Lymph Node Assay
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification (determination)
µg	micro gram
mN	milli-Newton
MN	micronuclei
MNIE	micronucleated immature erythrocytes
MRL	maximum residue limit or level
MS	mass spectrometry
MWHC	maximum water holding capacity
NESTI	national estimated short term intake
NIR	near-infrared-(spectroscopy)
nm	nanometer
NMR	nuclear magnetic resonance
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
OC	organic carbon content
OM	organic matter content
PD	proportion of different food types
PEC	predicted environmental concentration
PEC_{air}	predicted environmental concentration in air
PEC_{gw}	predicted environmental concentration in ground water
PEC_{sed}	predicted environmental concentration in sediment
PEC_{soil}	predicted environmental concentration in soil
PEC_{sw}	predicted environmental concentration in surface water
PF	processing factor
PHI	pre-harvest interval
pKa	negative logarithm (to the base 10) of the dissociation constant
PPE	personal protective equipment
ppm	parts per million (10-6)
ppp	plant protection product

PT	proportion of diet obtained in the treated area
PTU	propyl-thiouracil
QC	quality control
QSAR	quantitative structure-activity relationship
r2	coefficient of determination
RBC	red blood cell
RMS	rapporteur Member State
RPE	respiratory protective equipment
SFO	single first-order
STMR	supervised trials median residue
STP	sewage treatment plant
T_3	tri-iodothyroxine
T_4	thyroxine
TER	toxicity exposure ratio
TER_A	toxicity exposure ratio for acute exposure
TER_{LT}	toxicity exposure ratio following chronic exposure
TER_{ST}	toxicity exposure ratio following repeated exposure
TF	transfer factor
TLC	thin layer chromatography
TMDI	theoretical maximum daily intake
TPEM	two phase exponential model
TRR	total radioactive residue
TWA	time weighted average
UDS	unscheduled DNA synthesis
UV	ultraviolet
W/S	water/sediment
w/v	weight per volume
w/w	weight per weight
WBC	white blood cell
WHO	World Health Organisation
wk	week
yr	year