CONCLUSION ON PESTICIDE PEER REVIEW

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

Issued on 30 September 2008

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[1]. This Regulation requires the European Food Safety Authority (EFSA) to organise upon request of the EU-Commission a peer review of the initial evaluation, i.e. the Draft Assessment Report (DAR), provided by the designated rapporteur Member State and to provide within six months 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 for consultation of the Member States and to the sole applicant Bayer CropScience AG. 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 applicant 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 laid down in this report.

The conclusion was reached on the basis of the evaluation of the representative uses as fungicide as proposed by the notifier, which comprises seed treatment in barley against several agriculturally important diseases. Full details of the GAP can be found in the attached endpoints.
The specification for the technical material as a whole should currently be regarded as provisional (September 2008).

[1] 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)

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 and animal origin, soil and water, however for air, a method validated to LOQ of 0.6 µg a.s./m³ is required.

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 and kidneys. 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 any 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 and rabbits.
The agreed **acceptable daily intake** (ADI) was **0.00005 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 10. This was justified by the use of a lowest observed adverse effect level, the shallow dose-response in the study and the absence of mechanistic information. The agreed **acceptable operator exposure level** (AOEL) was **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 agreed **acute reference dose** (ARfD) was **0.015 mg/kg bw** based on the 4-week rat study and applying a safety factor of 100.
The agreed dermal absorption values to be used in the risk assessment were 2.4% for the concentrate and 2% for the contaminated grain dust. The operator exposure estimate during the seed treatment was above the AOEL with the SeedTropex model, but realistic field studies showed an exposure level up to 21% of the AOEL. Similarly, the exposure estimates for the worker loading and sowing treated seed was above the AOEL with the SeedTropex model, but below the AOEL with a field study (26%).

With regard to consumer exposure assessment, the nature and magnitude of residues in plant and animal commodities could not be sufficiently clarified by the submitted data on triazoxide applied as a seed treatment to barley.

Taking into account the toxicological profile of triazoxide and its metabolites, the meeting of experts in residues agreed on data gaps with regard to the nature of residues in the plant. No final residue definition for monitoring and risk assessment could therefore be agreed. In the submitted residue trials no residues of triazoxide were found above the LOQ of 0.05 mg/kg in grain and straw. However, it was agreed that the analytical method used in these trials was not validated at a sufficiently low LOQ to ensure that an exceedance of the ADI could be definitively excluded, and therefore new trials with a lower LOQ were required. Assuming residues of triazoxide were present in barley grain at the LOQ level of 0.05 mg/kg, the ADI was exceeded for one Member State diet in the EFSA PRAPeR model. The potential for residues being present in food of animal origin due to carry-over from treated straw has not been addressed, since no data on livestock was submitted due to residues being below the LOQ of 0.05 mg/kg in grain and straw in residue trials. However, given the very low ADI of triazoxide and its metabolites, and given the presence of total residues of 0.04 mg/kg in straw, the experts had concerns that transfer of toxicologically relevant residues from straw into livestock matrices may occur, even though at very low levels. An indicative exposure assessment, using the default residue value of 0.01 mg/kg for milk, showed that the ADI would be significantly exceeded for a number of European national and regional diets, and therefore further consideration of the issue of residues in animal products is required.

No concerns were identified with regard to residues in rotational crops, provided rotated cereals will be addressed with the required new data for the primary cereal crop.

In conclusion, the available metabolism and **residue data are not considered appropriate to conduct a robust consumer exposure and risk assessment** due to the uncertainties identified with regard to the nature of residues in plant commodities, and with regard to possible transfer of residues in animal products, and the need for a lower LOQ of the analytical method for the relevant analytes in studies on the magnitude of residues.

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). Degradation of triazoxide proceeds either through reduction to desoxy-triazoxide (M01)[2], or through production of triazoxide-amine (M02)[3]. Assessment based on the decline from the peak observed indicate that M01 was moderate persistent in soil ($DissT_{50\ lab}$ = 32.4 – 56.7 days), and M02 could be considered high to very high persistent (decline M02 $DissT_{50\ field}$ = 239 – 447 days; excluding UK field trial where no decline is observed). A kinetic assessment of laboratory data allowed the applicant to derive kinetic half-lives for M01, that

[2] M01: 7-chloro-3-imidazol-1-yl-1,2,4-benzotriazine
[3] M02: 7-chloro-1,2,4-benzotriazin-3-amine 1-oxide

are associated with a formation fraction of 1. 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.

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

Field studies are available, with some of them including measurements of the soil metabolites. Kinetic analysis of the field data presented by the applicant was discussed by the meeting of experts. The kinetic analysis was not fully accepted, and the need of considering formation fractions of 1 for further modelling based on this analysis was agreed. Analysis of the data based on the decline of M02 has been performed by the RMS, and the resulting half-lives (decline M02 $DissT_{50\ field}$ = 239 – 447 days; excluding UK field trial where no decline is observed) may be used in conjunction with the maximum observed of 18.7 % for exposure risk assessment. PECs soil presented in the DAR were calculated by the RMS for triazoxide and its soil major metabolites following standard procedures. Updated PECs soil with parameters agreed by the meeting of experts are reported in addendum 2 and do not result in a change of the risk assessment already performed.

According to the available studies, triazoxide may be considered as low to medium mobile in soil (K_{foc} = 245 – 1743 mL /g), desoxy-triazoxide (M01) may be considered slightly mobile (K_{foc} = 2053 – 4148 mL /g), and triazoxide-amine (M02) may be considered low to medium mobile (K_{foc} = 385.6 – 1709.0 mL /g). The RMS noted the narrow range of pH and the ionisable character of the metabolite triazoxide-amine (M02). Whereas a large margin of safety is considered to exist for the representative use proposed, further data could be needed if other uses at significant 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 triazoxide-oxone (M04)[4]. Triazoxide is rapidly photolysed in water (DT_{50} = 24.4 hours equivalent to 3.5 natural solar days at 33 ºN). An additional study indicates that 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 triazoxide-desoxyamino (M05)[5]. 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 desoxy-triazoxide in the water

[4] M04: 7-chloro-1,2,4-benzotriazin-3(4*H*)-one 1-oxide
[5] M05: 7-chloro-1,2,4-benzotriazin-3-amine

sediment systems. This kinetic analysis was only partially validated by the RMS (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 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 triazoxide-desoxy, respectively, based on results of Lienden system.

Input parameters to be used for FOCUS PEC_{SW} were discussed and agreed in the meeting of experts. After the meeting, the RMS has presented an addendum with new FOCUS SW (Step 1 and Step 2) for metabolite M01 and M02 following the approach agreed by the meeting. However, the new PECs calculated do not alter the outcome of the risk assessment already presented by the RMS in the DAR.

Three different approaches based on FOCUS GW to calculate PEC GW were presented in the DAR. The meeting of experts agreed on the approach presented under B.8.6.d for the parent compound, but disagreed with the formation fractions assumed for metabolites M01 and M02, for which a formation fraction of 1 had to be used. After the meeting the RMS presented a new groundwater assessment based on FOCUS PEARL v.3.3.3, and the input parameters agreed by the meeting of experts. Neither the parent compound, nor its major soil metabolites (M01 and M02) exceeded the trigger of 0.1 µg /L when the EU representative use (cereals seed treatment, 6 g a.s./ ha) is simulated. However, due to the low ADI determined for this substance, 10% of the ADI would be reached for adults, toddlers and bottle fed infants, if residue levels of 0.05 µg/L, 0.017 µg/L and 0.011 µg/L, respectively, of each component (triazoxide, M01 and M02) were present in the water. These levels were not exceeded in any of the scenarios simulated for the representative use in cereal seeds. Nevertheless, reliability and predictive capacity of FOCUS GW models is expected to be lower in this low range of concentrations. 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 endpoint, due to food avoidance (endpoint 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 time scale. The conclusion was supported by an additional assessment for a fast feeding granivorous bird, like the woodpigeon. In order to reach the $LD_{50,}$ woodpigeons would have to consume 2940 seeds (includes a 10-fold uncertainty factor). A long-term risk assessment on

reproductive birds was considered relevant for the spring use of triazoxide as seed treatment (the autumn use may also be reproductively relevant for birds in some southern Member States). 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 spring use.

The tier 1 acute risk assessment for granivorous mammals was found to be low. Further refinements were required to identify a low long-term risk to granivorous mammals. Refinements were based on wood mouse as focal species and on use of measured residue data (see birds above), resulting in a TER value of 0.64. Further refinements were required to address the long-term risk to granivorous mammals. Risk assessment of secondary poisoning and consumption of contaminated drinking water was considered not relevant.

Triazoxide is proposed to be classified as very toxic to aquatic organisms. The acute risk to aquatic organisms was assessed to be low. Further refinements were required to address the long-term risk to fish. The risk to sediment-dwellers from the metabolite M01, M02 and M05 was assessed as low.

The acute risk to earthworms was considered to be low. The long-term risk to earthworms needs further refinements to fully address the potential toxicity of residues in the soil matrix. As for other soil non-target macro-organisms, the risk to springtails was low for all potential soil residues, but it still remains to address the potential risk to soil litter degrading processes from triazoxide and the soil metabolites M01 and M02.

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 laying down the detailed rules for the implementation of the third stages of the work program referred to in Article 8(2) of Council Directive 91/414/EEC and amending Regulation (EC) No 451/2000, as amended by Commission Regulation (EC) No 1095/2007, regulates for the European Food Safety Authority (EFSA) the procedure of evaluation of the Draft Assessment Reports provided by the designated rapporteur Member State. Triazoxide is one of the 84 substances of the third stage, part B, covered by the Regulation (EC) No 1490/2002 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 Draft Assessment Report, 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 Draft Assessment Report. In accordance with Article 11(2) of the Regulation (EC) No 1095/2007, the revised version of the Draft Assessment Report was distributed for consultation on 6 November 2007 to the Member States and on 4 October 2007 to the sole applicant Bayer CropScience AG as identified by the rapporteur Member State.

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 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 the Member States in August 2008 leading to the conclusions as laid down in this report.

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

In accordance with Article 11(4) of the amended Regulation (EC) No 1490/2002, this conclusion summarises the results of the peer review on the active substance and the representative formulation

evaluated as finalised at the end of the examination period provided for by the same Article. A list of the relevant endpoints for the active substance as well as the formulation is provided in appendix 1.

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

- the comments received,
- the resulting reporting table (revision 1-1 of 4 March 2008)

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

- the reports of the scientific expert consultation,
- the evaluation table (revision 2-1 of 30 September 2008).

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

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 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*), and seed-borne net blotch (*Pyrenophora teres*) 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).

SPECIFIC CONCLUSIONS OF THE EVALUATION

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

The minimum purity of triazoxide could not be concluded on. There is no FAO specification available.

The PRAPeR 46 meeting of experts (May 2008) did not accept the technical specification for the active substance and some impurities based on quality control data, and proposed a data gap for the applicant to provide a new specification based on 5-batch analysis, or to provide more information on the QC data to support the specification. A revised specification has been submitted to the RMS, however, in view of the restrictions concerning the acceptance of new (i.e. newly submitted) studies after the submission of the DAR to EFSA, as laid down in Commission Regulation (EC) No. 1095/2007, the new studies could not be considered in the peer review.
A new data gap was also set for additional validation data for a method for an impurity specified above 1 g/kg. It should be noted that the validation study has been carried out, however, in view of the restrictions concerning the acceptance of new (i.e. newly submitted) studies after the submission of the DAR to EFSA, as laid down in Commission Regulation (EC) No. 1095/2007, the new studies could not be considered in the peer review.
Toluene was considered as relevant impurity in the technical material with a maximum level of 5 g/kg.

The specification for the technical material as a whole should currently be regarded as provisional (September 2008).
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 formulations.
The main data regarding the identity of triazoxide and its physical and chemical properties are given in appendix 1.

Adequate analytical methods are available for the determination of triazoxide in the technical material and in the representative formulation (HPLC-DAD), as well as for the determination of the respective impurities in the technical material (HPLC-DAD), however additional validation data were requested for an impurity specified above 1 g/kg (data has been submitted, but cannot be considered in the peer review process).
Sufficient test 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 triazoxide residues in food/feed of plant and animal origin, however a data gap was set for linearity data for barley straw and green material, and depending on the MRLs proposed, methods with lower LOQs might be required. It should be noted that the linearity data and a method with an LOQ of 0.001 mg/kg have been submitted to the RMS, however, in view of the restrictions concerning the acceptance of new (i.e. newly submitted) studies after the submission of the DAR to EFSA, as laid down in Commission Regulation (EC) No. 1095/2007, the new studies could not be considered in the peer review.

Residues of triazoxide in food of plant and animal origin can be monitored by HPLC-MS/MS with LOQ of 0.05 mg/kg (for milk the LOQ is 0.01 mg/l).

HPLC-MS/MS methods are available to monitor residues of triazoxide and its metabolites desoxy-triazoxide (M01)[6] and triazoxide-amine (M02)[7] in soil with LOQ of 0.001 mg/kg, and residues of triazoxide and its metabolite M01 in water with LOQ of 0.1 µg/l. However, due to the low ADI determined for this substance, 10% of the ADI would be reached for adults, toddlers and bottle fed infants if residue levels of 0.05 µg/L, 0.017 µg/L and 0.011 µg/L, respectively, of each component (triazoxide, M01 and M02) were present in the water, therefore a data gap for a method with a LOQ of at least 0.01 µg/L was identified.
Additional validation data for the monitoring method for the determination of the active substance in air was required, and a data gap was identified for an analytical method with an LOQ of 0.6 µg/m³. It should be noted that a such method has been submitted to the RMS, however, in view of the restrictions concerning the acceptance of new (i.e. newly submitted) studies after the submission of the DAR to EFSA, as laid down in Commission Regulation (EC) No. 1095/2007, the new studies could not be considered in the peer review.
Triazoxide residues in blood can be monitored by HPLC-MS/MS, with LOQ of 0.05 mg/l.

2. Mammalian toxicology

Triazoxide was discussed by the experts in mammalian toxicology in June 2008 (PRAPeR meeting 49, round 10, subgroup 2).
In the toxicological batches, most of the impurities were in 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.
Notwithstanding an acceptable level in the technical specification which does not raise any toxicological concern, the impurity 5 (toluene) should nevertheless be considered as relevant due to

[6] M01: 7-chloro-3-imidazol-1-yl-1,2,4-benzotriazine
[7] M02: 7-chloro-1,2,4-benzotriazin-3-amine 1-oxide

its reproductive toxicity (Repro. Cat. 3; R63), in order to be monitored closely in the technical specification.

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 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 and kidneys. 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, the final decision of classification will have to be taken 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 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 indicates 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. Considering the increased incidence of darkly coloured spleen without histopathological correlates, the increased relative spleen weight in interim females and some effects on the erythrocytes that were not clearly dose related, the experts could not agree on whether 1 ppm was a NOAEL or a LOAEL. Therefore, it was 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 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 weights in males and increased ovarian weights 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 a 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 agreed that triazoxide was likely to be found in milk and the meeting agreed to propose the classification **R64 May cause harm to breastfed babies**.

In the developmental studies, there were no signs of maternal toxicity in the rabbits, and a reduced bodyweight gain in the 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 none of 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 and long-term studies. Therefore no further testing is indicated.

2.8. FURTHER STUDIES

In the absence of any information on the metabolites, the 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 stated that no poisoning incidents are known to them. 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 meeting agreed with the proposed ADI of **0.00005 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 1000.

The additional safety factor of 10 was justified by the use of a LOAEL, the shallow 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 agreed to derive the AOEL from the 90-day rat study as proposed in the DAR, but with an additional correction for the bioavailability (50%). Therefore the resulting AOEL is **0.001 mg/kg bw/day** with the use of a safety factor of 100.

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 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 sowing treated seed (i.e. workers).

EFSA notes: The supported formulation is a combined product (tebuconazole + triazoxide). The presence and possible contribution of the second active substance to the toxicological burden will

have to be considered at member state level since there is no harmonized approach on how to perform the risk assessment for a combined product.

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 (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.

Worker exposure during seed loading/sowing

Based on Seed Tropex data, the exposure estimate during seed loading/sowing was above the AOEL, even 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.

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

° operator wearing standard protective garment i.e. coverall

°° operator wearing a single layer of clothing

Bystander exposure

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

3. Residues

Triazoxide was discussed by the experts in residues in June 2008 (PRAPeR meeting 50, round 10).

3.1. NATURE AND MAGNITUDE OF RESIDUES IN PLANT

3.1.1. PRIMARY CROPS

A metabolism study was conducted in cereals by applying phenyl ring labelled [^{14}C] triazoxide as a seed treatment to barley seed. The study was performed in the early 1980's, and at an application rate approximately matching the notified representative use (1.5 N). At harvest of the mature cereal crop the total radioactive residues (TRR; expressed as parent equivalent) in the grain and straw were <0.01 and 0.04 mg/kg respectively. In view of the low total residues in the plant samples a detailed investigation of the metabolism in the plant was not undertaken, and no metabolites were identified or characterised. An imidazole ring labelled triazoxide study for barley was not submitted because total residues in barley grain and straw have been demonstrated to be low in the phenyl ring labelled metabolism study. Based on the available data for barley the RMS proposed a default residue definition for both monitoring and risk assessment as triazoxide.

However, the meeting of experts PRAPeR 50 had a concern on whether non-identification of residues in the study was acceptable given the toxicological profile of triazoxide. It was noted that the ADI value was extremely low (0.00005 mg/kg bw/day) and that according to current guidelines the usual trigger values for identification, as applied in the study, may not be applicable for very hazardous compounds. Since there was no further identification in barley grain and straw, the experts had concerns if, despite of the low level of radioactivity, triazoxide or metabolites with similar toxicological properties could be present.

The available residue trial data did not provide conclusive support for addressing the concern. All grain and straw samples were analysed for triazoxide. In few trials also a metabolite desoxy-triazoxide[8] (M01) was analysed. Though no residues were found above the LOQ (0.05 mg/kg), it was agreed that the analytical method used in these trials was not validated at a sufficiently low LOQ. The experts noted that an assumed level of 0.05 mg/kg triazoxide in barley grain would already lead to an exceedance of the ADI in the consumer risk assessment using the EFSA PRAPeR model (see 3.3). The absence of triazoxide and/or metabolites at levels relevant with respect to consumer risk assessment could not be demonstrated by the submitted residue trial data, nor could any further information on the identity of residues in the crop be obtained.

The meeting on toxicology concluded that not only triazoxide was of concern, but all metabolites should be considered of comparable toxicity. This is mainly related to the fact that the mode of action of triazoxide is not known and therefore it is not known if the toxicity can be attributed to one chemical structure or a part of it. The consequence with regard to consumer risk assessment is likely

[8] M01: 7-chloro-3-imidazol-1-yl-1,2,4-benzotriazine

to be a total residue definition, including triazoxide and all of its metabolites in plants. For monitoring the definition might be pending the identification of a suitable marker compound.
The conclusion of the meeting on toxicology was reached after the discussion in the meeting of residues had been finalised, and thus the previous agreements by the experts in residues could not be reviewed in the light of the agreed position on comparable toxicity of metabolites and triazoxide. The experts had already identified a data gap for a new plant metabolism study and to perform a complete metabolite identification based on recent analytical methods in order to establish a metabolic degradation pathway of triazoxide in barley grain and straw. The study is also considered necessary to address rotated cereals metabolism (see 3.1.2 below).
Still, in the light of the decision of the meeting on toxicology EFSA consider that the data gap identified for a new plant metabolism study should remain in place as this is considered pertinent information for the evaluation of triazoxide with regard to residues in food and feed items.
As for the moment, the initially proposed plant residue definition, triazoxide per default, is provisional only and pending submission of further data that clarify the identity of residues in plant matrices.

A set of residue trials from northern Europe was submitted with the dossier, the majority of them were carried out in the 1980's. 11 residue trials in barley and a total of 7 trials in oat, rye and wheat were considered acceptable for evaluation, since they were conforming to GAP, reported in sufficient detail and supported by valid storage stability data. As mentioned above in this chapter the LOQ of the analytical methods for triazoxide was 0.05 mg/kg in both grain and straw. According to the agreed approach in consumer risk assessment by assuming residues in barley grain were at LOQ level, an exceedance of the ADI cannot be excluded using the EFSA PRAPeR model. Therefore, the experts unanimously agreed that residues trials with a lower LOQ are necessary.
The applicant indicated in the evaluation table that new residue trials conducted in 2007 with a lower LOQ of 0.001 mg/kg were available, but not submitted to the RMS. The meeting of experts concluded it could be useful to require these new residue trials in order to possibly perform a new dietary risk assessment with an MRL at an LOQ lower than 0.05 mg/kg. This agreement was reached by the experts without having notice of the later conclusion of the meeting on toxicology with regard to triazoxide metabolites. However, the experts anticipated that metabolites would have to be taken into account in the risk assessment for their toxicological properties, and proposed the following options to tackle this situation and to address the magnitude of relevant residues accordingly: When the new metabolism study is available, an option could be to derive a factor to convert from the amount of triazoxide to the total amount of toxicologically pertinent compounds, if the use of such conversion factor would prove feasible in the context of pre- and post authorisation risk assessment. A second option could be re-analysis of the stored samples from the new residue trials of 2007, which are believed to be still available. It is noted that the proposals are suggestions only. Primarily, the outcome of the new plant metabolism study will need careful consideration before further approaches can be deliberated.

Data on the nature and magnitude of residues in processed products were not submitted, again for the reason of residues in the grain being below the LOQ of the analytical method of 0.05 mg/kg. However, the EC guidance document on processing studies (7035/VI/95 rev.5) is very clear with respect to (non-)applicability of the waiver value for pesticides with a low ADI. Though not explicitly discussed by the meeting of experts, EFSA notes that a decision of whether or not further investigation will be required on distribution, enrichment or dilution of residues in processed cereal products is for the present pending the submission of data addressing the identified data gaps on nature and level of residues in the raw agricultural commodity.

3.1.2. SUCCEEDING AND ROTATIONAL CROPS

Triazoxide may be considered to be high to very high persistent in soil (for details refer to chapter 4.1).

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 as/ha (approx. 3 N). The notified application rate of triazoxide to barley seed equates to a field rate of 6 g as/ha. 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 plant 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 meeting of experts that in the study in rotational crops 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 the necessary 3 crop categories being 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 document 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 4.1), it does not seem necessary to require further rotational crop data at plant-back intervals shorter than the one studied, since 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 document.

The meeting noted that, considering the slightly higher application rate on barley compared to the supported use, the behaviour of triazoxide residues in soil 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. As for cereals, this is expected to be finally addressed with the required new data for the primary crop (see chapter 3.1.1 above). The experts also agreed that, according to the currently available data, residues in straw from rotated cereals may occur and should be considered for the livestock dietary burden assessment.

3.2. NATURE AND MAGNITUDE OF RESIDUES IN LIVESTOCK

No data were submitted to study the nature and magnitude of residues in livestock, since triazoxide levels in potential feed items (barley grain and straw) in residue trials were below the limit of quantification at harvest. However, as already previously stated the LOQ of 0.05 mg/kg was considered by the experts to be not sufficiently low for risk assessment purposes.

Given the toxicological properties of triazoxide the usual trigger values as set in the guidance document[9] may not be applicable. Considering total residues in barley straw (0.04 mg/kg) in the cereal metabolism study, the experts had concerns that a transfer of those residues in straw in livestock matrices (e.g. milk) may occur, even though at very low levels.

Currently there is insufficient data to conclude this area of assessment and further investigation will be necessary when the nature of residues in cereal matrices has been clarified. Subsequently livestock exposure to residues relevant for risk assessment and the potential of carry over and/or accumulation of these residues in food of animal origin will have to be addressed by the applicant. In particular residues in straw from primary and rotated cereal crops should be taken into account for the livestock dietary exposure assessment.

The decision whether a livestock study should be required is pending the assessment of the new plant metabolism study. The experts also expected a method of analysis for animal matrices with an LOQ lower than 0.01 mg/kg.

Moreover, the experts raised a question concerning animal health when livestock is exposed to residues from triazoxide use at levels found in straw in the cereal metabolism study, and this question may also have to be addressed when the new cereal metabolism study is available.

3.3. CONSUMER RISK ASSESSMENT

The hazard assessment defined the relevant compounds as triazoxide and its metabolites.

With regard to consumer exposure assessment, the nature of residues in edible plant and animal commodities has not been sufficiently clarified. The meeting of experts in residues concluded that the residue definition for monitoring and risk assessment proposed by the RMS as triazoxide by default can only be considered a provisional definition and should be subjected to re-evaluation. Metabolites,

[9] Guidelines for the generation of data concerning residues as provided in Annex II part A, section 6 and Annex III, part A, section 8 of Directive 91/414/EEC concerning the placing of plant protection products on the market, Appendix F: Metabolism and distribution in domestic animals, Doc. 7030/VI/95 rev.3

if present, need to be taken into account in the residue definition. Therefore, a final definition is pending the assessment of the required new cereal metabolism study.

The chronic consumer risk assessment originally conducted by the RMS used default assumptions about residues in barley grain (only triazoxide present at LOQ level 0.05 mg/kg) and the WHO cluster diets to estimate the TMDI, and UK consumption data to estimate the UK NEDI. In both assessments intake estimates were below the ADI of 0.00005 mg/kg bw/day in all cases (highest: WHO cluster diet E, 81%). The meeting of experts noted that with the same assumptions, but using consumption data from the EFSA PRAPeR model, the ADI was exceeded in one diet (124%, Irish adult). Potential residues in food of animal origin have not been considered in neither of these estimates.
However, such an estimate was done by the experts in the meeting. Assuming a maximum total residue level of 0.01 mg/kg triazoxide equivalents for barley grain (as reported in the radiolabel metabolism study), this resulted in no exceedance of the ADI using the EFSA PRAPeR model. When, in addition, the LOQ for milk of 0.01 mg/kg was applied in an indicative exposure assessment to account for a potential carry-over of residues from straw in animal matrices, was the ADI exceeded for a number of national and regional diets in the EFSA PRAPeR model (France, UK, The Netherlands, Denmark, Spain, Sweden, Finland, WHO EU regional diet and cluster diet D), in particular for children with a highest intake for the French toddler (793% ADI). The result highlights the importance of further considerations with regard to residues in animal products, even at very low levels.

It should be noted that there is uncertainty in the approach of assuming the total residue level in grain and straw in the radiolabel metabolism study would result in the maximum possible exposure of consumers and livestock, respectively, since these figures are based on a single study only. Moreover, the extent of consumer exposure through potential transfer of residues in food of animal origin, e.g. in milk is very difficult to assess with the currently available data.
In an acute dietary risk assessment with the UK national model and the EFSA PRAPeR model no exceedance of the ARfD of 0.015 mg/kg bw/day was observed for barley grain and for food of animal origin when the respective LOQ is applied in the assessment.

It should be noted that both chronic and acute consumer exposure assessment are provisional. Without further data as identified by the meeting of experts it is also not possible to refine the current provisional estimates, in particular the chronic intake assessment, with regard to the notified use of triazoxide in barley.

In conclusion, the available metabolism and residue data are **not considered sufficient and appropriate to conduct a robust consumer exposure and risk assessment** due to the

- uncertainty identified with regard to the nature of residues in plant commodities

- uncertainty identified with regard to possible transfer of residues in animal products
- need for a lower LOQ of the analytical method for the relevant analytes in studies on the magnitude of residues.

Moreover, it should be noted that the consumer risk assessment as presented above does not take into account residues of the second active substance in the formulation, tebuconazole.

The current use, corresponding to a application rate of 6 g as/ha, is not expected to lead to residue levels in groundwater above 0.1 µg/L for triazoxide and the two groundwater metabolites M01 and M02[10] (refer to chapter 4.2.2). However, EFSA considers it important to inform risk managers that, given the low ADI of triazoxide and metabolites, in intake estimates with ground water used as drinking water, 10% of the ADI would be reached for adults, toddlers and bottle fed infants if residue levels of 0.05 µg/L, 0.017 µg/L and 0.011 µg/L, respectively, of each component (triazoxide, M01 and M02) were present in the water. The estimates were carried out according to the WHO Guideline on drinking water quality. This information might affect the decision regarding an appropriate LOQ of the monitoring analytical method for triazoxide, M01 and M02 in groundwater, in order to ensure a high level of consumer protection.

3.4. PROPOSED MRLS

Based on the available data it is currently only possible to propose provisional MRLs for triazoxide in barley and in food of animal origin at the respective LOQ of the analytical method for monitoring/enforcement (barley and food of animal origin except milk 0.05 mg/kg; milk 0.01 mg/kg). It is noted that in a risk assessment with these provisionally proposed MRLs the ADI will be significantly exceeded for a number of European consumers.

4. Environmental fate and behaviour

Fate and behaviour of triazoxide in the environment was discussed in the PRAPeR 47 meeting of experts (May 2008) on basis of the DAR (June 2007) and the updated evaluation table (March 2008). After the meeting, the RMS produced addendum 1 (June 2008) that includes some amendments and additions to chapter B.8 of the DAR. All fate and behaviour studies were performed with triazoxide [^{14}C] radiolabelled at the phenyl ring. The justification for not performing studies with substance labelled at the imidazol ring presented in the dossier was found acceptable.

[10] M02: 7-chloro-1,2,4-benzotriazin-3-amine 1-oxide

4.1. FATE AND BEHAVIOUR IN SOIL

4.1.1. ROUTE OF DEGRADATION IN SOIL

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. Degradation proceeds initially either through reduction to produce **triazoxide-desoxy**[11] (M01: max. 12.8 % AR at 30 DAT), or through loss of the imidazole moiety to produce triazoxide-amine[12] (M02: max. 9.0 AR at 3 DAT). 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).

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 d 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. 28.3 % 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 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

Rate of degradation in soil was investigated in the same studies presented in the route section. 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).

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 moderate 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, together with a maximum relative M01 amount of 17.7 % (on molar basis, from maximum observed in field studies) of parent applied.

[11] M01: 7-chloro-3-imidazol-1-yl-1,2,4-benzotriazine
[12] M02: 7-chloro-1,2,4-benzotriazin-3-amine 1-oxide

A field dissipation study, encompassing four bare soil trials in different sites of northern-mid Germany (pH 5.5 – 6.5; OC 1.5 – 2.5 %), is available in the dossier. The half-lives were recalculated with a non-linear regression method to first order kinetics ($DissT_{50}$ = 54 – 71.1 days; only three of the four values were considered reliable). However, the conditions under which the trials had been performed were very different than the representative use (1000 fold application rate, application timing), and the report had some deficiencies (lack of climatic data) that, even if do not completely invalidate the study, justify to disregard its results for the EU risk assessment.

An additional field study was 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.

The applicant presented a kinetic analysis of the field dissipation data to derive degradation rates and formation fractions of the parent and the metabolites. The meeting of experts discussed the reliability of this kinetic analysis. It was noted that the data has been fitted directly in the mass base. However, after the fitting, the mass formation fraction of the metabolites has been transformed to express it in molar base. Nevertheless, the methodology used to derive the formation fractions was not transparently reported, especially with respect to the formation fractions calculated with "hockey stick" model for the parent and SFO for the metabolite. With respect to the metabolite M01 the meeting agreed that the degradation rate has been calculated assuming a formation fraction of 1 and that, consequently, a formation fraction of 1 needs to be also assumed in the modelling calculations. Also the meeting agreed that the formation fraction of 1 has to be used for metabolite M02, if no satisfactory justification of the formation fraction presented in the kinetic analysis is provided.

After the meeting of the experts, the RMS calculated for M02 new decline half-lives from the maximum observed in the field studies. According to these new values, M02 could be considered high to very high persistent (decline M02 $DT_{50\ field}$ = 239 – 447 days; excluding UK field trial where no decline is observed). Whereas not fully peer reviewed, these half-lives have been derived following the procedure agreed by the meeting of experts and the calculations transparently reported in the addendum of June 2008; therefore, they may be used in conjunction with the maximum observed of 18.7 % for exposure risk assessment.

PECs soil presented in the DAR were calculated by the RMS for triazoxide and its soil major metabolites following standard procedures. Calculations have been updated by the RMS in addendum 2 with the input parameters agreed in the experts meeting. An application rate of 6 g / ha and realistic worst case half-lives and maximum relative amount observed for triazoxide (DT_{50} = 325.3 days, from worst case field DT_{90} divided by 3.32), triazoxide-desoxy (M01; DT50 = 56.7 d; max. field 17.7 %) and triazoxide-amine (M02; DT_{50} = 313 d; max. field 18.7 %). The resulting new values do not change the outcome of the risk assessment already presented in the DAR. Since DT_{90} of triazoxide and metabolite triazoxide amine is above 90 days, the RMS also calculated accumulation of these substances in soil, and the maximum amount of M01 that may be expected to be formed from the maximum accumulated parent.

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 – 6.5; OC 0.8 – 2.1 %; clay 5.0 – 12.0 %) was performed with 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 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 proposed, further data could be needed if other uses at significant higher application rates are applied for in the future.

4.2. FATE AND BEHAVIOUR IN WATER

4.2.1. SURFACE WATER AND SEDIMENT

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 triazoxide-oxone[13] (M04; max. 97.3 % after 30 days).

Aqueous photolysis of triazoxide under artificial simulated sunlight (Xe lamp filtered for $\lambda < 290$ 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 triazoxide-desoxyamino[14] (M05; max = 49.7 % 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, 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.

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 (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 (M01; max. 47.4 % AR in the sediment after 30 days

[13] Triazoxide-oxone (M04): 7-chloro-1,2,4-benzotriazin-3(4*H*)-one 1-oxide
[14] Triazoxide-desoxyamino (M05): 7-chloro-1,2,4-benzotriazin-3-amine

based on TLC analysis) and M05 (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 = 1.5 % 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 by the RMS (only whole system results for the Lienden system were confirmed). For the IJzendoorn system, no reliable whole system half-lives for parent and 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 Lienden system.

New PEC_{SW} had been presented by the applicant before the meeting of experts; however, the approach and the input parameters used were not agreed by the meeting. Input parameters to be used for FOCUS PEC_{SW} were discussed in the meeting of experts. The experts were in favour of using the geometric mean of normalised field soil DT_{50} (approach presented in B.8.6 b in the DAR). Input parameters and resulting PEC_{SW} for the parent triazoxide were agreed by the meeting. Regarding M01, it was agreed that a new calculation using the decline DT_{50} observed from maximum (not degradation) in laboratory studies, together with the maximum observed in the field studies (17.7 % of parent) should be used. Also the experts noted that it is not possible to determine the rate of decline of M01 in field studies, since no decline is observed. Regarding M02, a consistent approach was agreed. The decline of M02 had to be calculated from soil field studies, and the result used in FOCUS PEC_{SW} calculation together with the maximum relative amount observed in the field (18 % of parent). For M05 the input parameters already used in the DAR under B.8.6 b) were confirmed by the meeting of experts. After the meeting, the RMS has presented an addendum with new FOCUS SW (Step 1 and Step 2) for metabolite M01 and M02 following the approach agreed by the meeting. However, the new PECs calculated do not alter the outcome of the risk assessment already presented by the RMS in the DAR.

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

Three different approaches based on FOCUS GW to calculate PEC GW were presented in the DAR. The meeting of experts agreed on the approach presented under B.8.6.d for the parent compound, but disagreed with the formation fractions assumed for metabolites M01 and M02. For these, the meeting agreed that, based on available data, formation fraction of 1 had to be used. After the meeting the RMS presented a new groundwater assessment based on FOCUS PEARL v.3.3.3 and the input parameters agreed by the meeting of experts. Neither the parent nor its major soil metabolites M01 and M02 exceeded the trigger of 0.1 µg / L when the EU representative use (cereals seed treatment, 6 g a.s. / ha) is simulated. However, due to the low ADI determined for this substance, 10% of the ADI

would be reached for adults, toddlers and bottle fed infants if residue levels of 0.05 µg/L, 0.017 µg/L and 0.011 µg/L, respectively, of each component (triazoxide, M01 and M02) were present in the water (see point 3.3 above). According to the model calculations available these levels were not exceeded in any of the scenarios simulated for the representative use in cereal seeds (for all three components < 0.001 µg/L). Nevertheless, reliability and predictive capacity of FOCUS GW models is expected to be lower in this low range of concentrations.

4.3. FATE AND BEHAVIOUR IN AIR

Triazoxide is not expected to significantly volatilize based on its physical and chemical properties (Henry Law constant = 7.3 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 in air.

5. Ecotoxicology

Triazoxide was discussed in the PRAPeR 48 meeting of ecotoxicology experts (subgroup 1) in May 2008, on the basis of the DAR (June, 2007).

Triazoxide is the active substance in the fungicidal formulation "RAXIL S FS 040". It is a flowable concentrate containing 20 g triazoxide/l and 20 g tebuconazole/l. The representative use of "RAXIL S FS 040" is a seed dressing applied at 3 g a.s./100 kg seed (equivalent to 6 g a.s./ha) on spring and winter barley.

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 presents 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. The RMS therefore proposed to use surrogate LDD_{50} 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/d was identified, based on the available reproduction study with Japanese quail (*Coturnix coturnix japonica*). The risk to birds and mammals was assessed in accordance with the Guidance Document for birds and mammals[15]. 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 believed that the margin of safety would cover the uncertainty related to the derivation of the short-term toxicity endpoint. Further refinements were

[15] Guidance Document on Risk Assessment for Birds and Mammals (SANCO/4145/2000)

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)[16], that yellowhammer may consume up to 1/3 of the 159 seeds on 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 in effect 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. The RMS suggested that spillages could be risk managed using appropriate labelling/user awareness campaigns. In consequence, birds in the wild 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 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 time scale was considered to be low for granivorous birds. In the refined long-term risk assessment the RMS considered that the autumn use of triazoxide as seed dressing in northern Member States would be outside the breeding season. The potential risk could be considered as low,

[16] Prosser P (1999): Project PN0907: Potential Exposure Of Birds To Treated Seeds. Final milestone report (revised March 2001). CSL, Central Science Laboratory, Sand Hutton, York UK

whereas this would not be the case for use in spring (or the autumn use in southern Member States). The long-term risk assessment was 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. Use of yellowhammer and woodpigeon as focal species was agreed by the RMS. 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). Refinements of the PT and PD factor would require further supporting data. Experts in PRAPeR 48 agreed to the risk assessment for birds. Further refinement was needed to address the long-term risk to granivorous birds from use of triazoxide as seed dressing on barley in spring (and possibly in autumn in southern Member States as birds here may also reproduce at this time of year).

In addition to the acute and long-term mammalian toxicological endpoints for triazoxide, a feeding study on house mice (*Mus musculus*) was provided by the applicant, to support a repellency factor. The RMS, however, concluded that no significant repellency factor could be derived from the study. The Tier 1 risk assessment for a granivorous mammal 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). The RMS 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 proposed use on spring sown barley would however require further consideration. Hence, the suggested refinement of the long term risk applied only to the proposed use in the spring. 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. Refinement of avoidance, dehusking, PD- and PT-factors proposed by the applicant was not accepted by the RMS, and would require further supportive data. The revised risk assessment gave a TER value of 0.64, indicating a need for further refinements.

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.

No specific toxicity studies were submitted for metabolites. Plant residue studies indicate that triazoxide was of low systemicity and would therefore not be expected to result in any significant residue in young plants. The two major soil metabolites M01 and M02 were predicted to be present in soil at lower levels than the parent triazoxide (Section B.8.3). Metabolite M01 has a $logP_{ow}$ of <3.0 and was therefore not expected to bio-accumulate. The $logP_{ow}$ for 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 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 contamination of drinking 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 endpoint 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 normal use it would not be expected to contaminate surface waters directly. Moreover, 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. This opinion was agreed in the meeting of experts. Based on FOCUS Step 2 PECsw estimations, all the acute TERs were above the Annex VI acceptable 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 section 4.2.1).
A chronic risk assessment to aquatic organisms was not provided in the DAR, as no chronic studies were available. To consider the chronic risk to aquatic organisms to be low, the RMS required further evidence to support a short duration of exposure. The chronic risk assessment was discussed in the meeting of experts. Since there was only a small margin of safety from the acute test (fish TER = 154), and no information about long term exposure, the meeting was of the opinion that an additional chronic study was needed for fish to address potential chronic risk[17].

The risk to aquatic organisms from the minor (<10%) water phase metabolites M01 and M05, and the soil metabolite M02 was assessed based on surrogate data of 10 times higher toxicity than the parent triazoxide toxicity and FOCUS Step 2 PECsw calculations. TER values were fare above the Annex VI trigger and the risk to aquatic organisms from metabolites was considered to be very low.

In sediment, M01 was defined as major, and it could not be concluded that M05 would not occur at >10%. For M01 a low risk to sediment-dwelling organism was predicted, based on a sediment-spiked Chironomid study. M05 represents a further degradation step of M01, and was predicted to occur at lower concentrations than this metabolite, the risk to sediment-dwelling organisms from M05 was therefore considered to be covered by the assessment for M01. Additionally, the risk from soil metabolite M02 was considered to be addressed by the risk assessment to M01, based on the facts that

[17] During the 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 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.

M02 represents a degradation step from M01 and the predicted sediment concentration was very similar to the estimated concentration of M01.

Bio-accumulation was not considered an issue, as $logP_{ow}$ is less than 3.

5.3. RISK TO BEES

Oral and contact toxicity of technical triazoxide to bees was low, based on the available data. The hazard quotients were well below the Annex VI trigger indicating a negligible risk. No further data or refinements were considered necessary. As "RAXIL S FS 040" also contains tebuconazole, Member State should ensure that the risk to bees from this component of the formulation should also indicate low risk before granting any authorisations, subsequent to a possible Annex I inclusion of tebuconazole.

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 6g 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 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 was 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 bileneata*), the carabid beetle (*Poecilus cupreus*) and the wolf spider (*Pardosa spp*). These additional species were exposed to seeds treated with the formulation (RAXIL S FS 040) in the range of the expected rate of use. Effects on relevant endpoints (i.e. mortality, feeding capacity or reproduction) did not exceed the Annex VI trigger limit of 50%. In addition, a study was also conducted to demonstrate the toxicity of technical triazoxide to the springtail (*Folsomia candida*). The TER value of 31250, based on a NOEC value from the study and a standard PECsoil calculation, indicated a negligible risk to this soil-dwelling non-target organism. The higher tier studies provided were considered to follow the recommendations of the terrestrial guidance document[18] for seed treatment. 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 at the proposed EU GAP.

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 a peak plateau soil concentration of 0.015 mg a.s./kg d.w. soil, TER values for technical triazoxide, "RAXIL S FS 040",

[18] Guidance Document on Terrestrial Ecotoxicology Under 91/414/EEC (SANCO 10329/2002)

M01 and M02 were all several orders of magnitudes above the Annex VI trigger, suggesting 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 indicated that the risk from a single drilling of treated seed was low, as no adverse effects on reproduction or sub-lethal effects were reported, when using seed drilled at a rate of 950 kg/ha. However, the study did not fully address the potential toxicity of residues in the soil matrix. Further consideration of the potential risk from accumulated residues of triazoxide and the two main soil metabolites M01 and M02 were considered necessary, before it could be concluded that the long term risk to earthworms would be low. Overall, it was concluded that the acute risk to earthworms was low from the intended use of triazoxide and that the long-term risk needs further refinements to fully address the potential toxicity of residues in the soil matrix.

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

Triazoxide is potentially persistent in soil having a non-normalised DT_{90} value of >365 days. It could not be stated with certainty, that M01 and M02 will not persist with DT_{90} >1 year in soil (see section 4.1.2). For triazoxide, soil metabolite M01 and "RAXIL S FS 040", a low risk to the springtail (*Folsomia candida*) was identified, using laboratory reproduction studies and worst case PECsoil values. TERs for triazoxide, metabolite M01 and "RAXIL S FS 040" were order of magnitudes above the Annex VI trigger. 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. A soil functionality test (litter bag study) conducted using "RAXIL S FS 040" treated seed was submitted. The relevance of this study could not be established as it was unclear whether the litter bags had been sufficiently exposed to triazoxide. Therefore, it still remains to address the potential risk to soil litter degradation processes from triazoxide. In addition, the potential risk to soil litter degradation processes from the two major soil metabolites M01 and M02 needs to be addressed. Overall, it was concluded that the risk to springtails was low for all potential soil residues, but it still remains to address the potential risk to soil litter processes from triazoxide and the soil metabolites M01 and M02.

5.7. RISK TO SOIL NON-TARGET MICRO-ORGANISMS

Compared to the control, technical triazoxide and M01 had no effects >25% after 28 days on nitrogen transformation at a soil concentration of 0.039 mg a.s./kg soil (exceeds the PEC plateau concentration expected from the intended 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 proposed rate. A low risk to soil non-target micro-organism was expected, based on the data presented and the intended use.

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

According to the terrestrial guidance document non-target plants are defined as non-crop plants located outside the treatment area. Given the intended 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 intended 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 requirement to provide information to fulfil Annex point (II A 8.7) has been met, and the risk to biological methods of sewage treatment was considered to be low from the intended use.

6. Residue definitions

Soil

Definition for risk assessment:	triazoxide, M01and M02.
Definition for monitoring:	triazoxide, M01and M02 (metabolites should be included pending long term risk assessment for earthworms and soil microorganisms).

Water

Ground water

Definition for exposure assessment:	triazoxide, M01 and M02
Definition for monitoring:	triazoxide (based on the representative use in barley seed treatment, may need to be revisited if other uses are applied for).

Surface water

Definition for risk assessment:	triazoxide
Definition for monitoring:	triazoxide

Air

Definition for risk assessment:	triazoxide
Definitions for monitoring:	triazoxide

Food of plant origin

Definition for risk assessment:	**provisional proposal**: per default triazoxide; however a new metabolism study is required to review the residue definition for the inclusion of metabolites
Definition for monitoring:	**provisional proposal**: per default triazoxide; however a new metabolism study is required to review the residue definition

Food of animal origin

Definition for risk assessment:	**open**, assessment pending the review of plant metabolism
Definition for monitoring:	**open**, assessment pending the review of plant metabolism

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

Soil

Compound (name and/or code)	Persistence	Ecotoxicology
triazoxide	High to very high persistent ($DT_{50\ lab\ (biphasic\ kinetic,\ overall)}$ = 208 – 278 d).	The acute risk to earthworms was considered to be low, as was the risk to springtails and soil non-target micro-organisms. The long-term risk needs further refinements to fully address the accumulation potential of triazoxide. The potential risk to soil litter processes needs to be addressed.
M01	Moderate persistent (decline $DT_{50\ lab}$ = 32.4 – 56.7 d)	The acute risk to earthworms was considered to be low, as was the risk to springtails and soil non-target micro-organisms. The chronic risk to earthworms and the potential risk to soil litter processes needs to be addressed.
M02	High to very high persistent (decline $DT_{50\ field}$ = 239 – 447 d)	The acute risk to earthworms was considered to be low, as was the risk to springtails and soil non-target micro-organisms. The chronic risk to earthworms and the potential risk to soil litter processes needs to be addressed.

Ground water

Compound (name and/or code)	Mobility in soil	> 0.1 µg / L 1m depth for the representative uses (at least one FOCUS scenario or relevant lysimeter)	Pesticidal activity	Toxicological relevance	Ecotoxicological activity
triazoxide	low to medium mobile (K_{foc} = 245 – 1743 mL / g)	FOCUS PEARL v.3.3.3: No (< 0.001 µg / L in all scenarios simulated) (based on the representative use as cereals seed treatment, 6 g/ha)	Yes	Yes	Yes
M01	slightly mobile (K_{foc} = 2053 – 4148 mL / g)	FOCUS PEARL v.3.3.3: No (< 0.001 µg / L in all scenarios simulated) (based on the representative use as cereals seed treatment, 6 g/ha)	No	Yes	No
M02	low to medium mobile (K_{foc} = 385.6 – 1709.0 mL / g).	FOCUS PEARL v.3.3.3: No (< 0.001 µg / L in all scenarios simulated) (based on the representative use as cereals seed treatment, 6 g/ha)	No	Yes	No

Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Triazoxide (surface water and sediment)	Triazoxide is very toxic to aquatic organisms. The acute risk from intended use was considered to be low. The long-term risk to fish needs to be addressed further.
M01 (sediment only)	No risk to sediment dwellers.
M02 (sediment only)	No risk to sediment dwellers.
M05 (sediment only)	No risk to sediment dwellers.

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

- A revised technical specification was identified as a data gap (relevant for all representative uses evaluated, data gap identified by PRAPeR 46 meeting of experts (May 2008), submitted to RMS in July 2008, however in view of the restrictions concerning the acceptance of new (i.e. newly submitted) studies after the submission of the DAR to EFSA, as laid down in Commission Regulation (EC) No. 1095/2007, the new studies could not be considered in the peer review refer; to chapter 1)
- Additional validation data for a method for an impurity specified above 1 g/kg (relevant for all representative uses evaluated, data gap identified in the PRAPeR 46 meeting of experts (May 2008), data already submitted, however in view of the restrictions concerning the acceptance of new (i.e. newly submitted) studies after the submission of the DAR to EFSA, as laid down in Commission Regulation (EC) No. 1095/2007, the new studies could not be considered in the peer review refer; refer to chapter 1)
- Linearity data for barley straw and green material were identified as a data gap (relevant for all representative uses evaluated, data gap identified in the DAR, data already submitted, however in view of the restrictions concerning the acceptance of new (i.e. newly submitted) studies after the submission of the DAR to EFSA, as laid down in Commission Regulation (EC) No. 1095/2007, the new studies could not be considered in the peer review refer; refer to chapter 1)
- Analytical method for the determination of the compounds in the residue definition in water with an LOQ of 0.1 µg/L was identified as a data gap (relevant for all representative uses evaluated, data gap identified by EFSA after the expert meetings (September 2008). Date of submission unknown, refer to chapter 1 and 4)
- Validated analytical method for the active substance in air with an LOQ of 0.6 µg/m³ was identified as a data gap (relevant for all representative uses evaluated, data gap identified in the PRAPeR 46 meeting of experts (May 2008), study submitted to the RMS in July 2008, however in view of the restrictions concerning the acceptance of new (i.e. newly submitted) studies after the submission of the DAR to EFSA, as laid down in Commission Regulation (EC) No. 1095/2007, the new studies could not be considered in the peer review; refer to chapter 1)
- A new metabolism study in barley is required to address primary crop metabolism (relevant for all representative uses evaluated; the applicant has confirmed that a study is on-going and should be completed in September 2008; data gap identified by the PRAPeR 50 meeting of experts in June 2008; refer to point 3.1.1)
- The primary crop metabolism study is also required to address rotated cereals metabolism. (relevant for all representative uses evaluated; the applicant has confirmed that the primary crop study is on-going and should be completed in September 2008; data gap identified by the PRAPeR 50 meeting of experts in June 2008; refer to point 3.1.2)

- The requirement for a new livestock metabolism study is pending the assessment of the new plant metabolism study (relevant for all representative uses evaluated; the applicant has confirmed that the primary crop study is on-going and should be completed in September 2008; data gap identified by the PRAPeR 50 meeting of experts in June 2008; refer to point 3.2)
- Residue trials in barley with a sufficiently low LOQ of the analytical method (relevant for all representative uses evaluated; residue trials with a lower LOQ of 0.001mg/kg was submitted to the RMS in July 2008. In view of the restrictions concerning the acceptance of new (i.e. newly submitted) studies after the submission of the DAR to EFSA, as laid down in Commission Regulation (EC) No. 1095/2007, this new study could not be considered in the peer review; data gap identified by the PRAPeR 50 meeting of experts in June 2008; refer to point 3.1.1)
- A refinement of the long-term risk assessment for granivorous birds exposed to 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 all representative uses evaluated, with the exception of autumn use in northern MSs which would be outside the breeding season; submission date proposed by the applicant: unknown; data gap identified in the DAR and agreed during the peer-review; refer to point 5.1)
- A refinement of the long-term risk assessment for granivorous mammals exposed to 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 all representative uses evaluated, with the exception of autumn use in northern MSs which would be outside the breeding season; submission date proposed by the applicant: unknown; data gap identified in the DAR and agreed during the peer review; refer to point 5.1)
- A chronic study with fish is required to address the long-term risk (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; data gap identified during the PRAPeR 48 meeting of experts; refer to point 5.2)
- Further refinements of the long-term risk to earthworms are required to address the potential toxicity of all residues in the soil matrix (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown (The applicant has submitted two new earthworm reproduction studies with triazoxide and MO1 to the RMS in November 2007. In view of the restrictions concerning the acceptance of new (i.e. newly submitted) studies after the submission of the DAR to EFSA, as laid down in Commission Regulation (EC) No. 1095/2007, these new studies could not be considered in the peer review; level 4 requirement; refer to point 5.5)
- It remains to address the potential risk to soil litter degradation processes from triazoxide and the two major soil metabolites M01 and M02 (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown (The applicant has submitted a new organic matter breakdown study using a formulated product to the RMS in April 2008. In view of the restrictions concerning the acceptance of new (i.e. newly submitted) studies after the submission of the DAR to EFSA, as laid down in Commission Regulation (EC) No. 1095/2007,

this new study could not be considered in the peer review); level 4 requirement; refer to point 5.6)

CONCLUSIONS AND RECOMMENDATIONS

Overall conclusions

The conclusion was reached on the basis of the evaluation of the representative uses as fungicide as proposed by the applicant for seed treatment on winter and spring barley, against several agriculturally important phytopathogens. For full details of the GAP please refer to the attached endpoints.

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 as a whole should currently be regarded as provisional (September 2008).

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 products is possible.

Adequate methods are available to monitor all compounds given in the respective residue definitions in food/feed of plant and animal origin, soil and water, however for the air a method validated to LOQ of 0.6 µg a.s./m³ is required.

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 and kidneys. 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 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 and rabbits.

The agreed **acceptable daily intake** (ADI) was **0.00005 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 10. This was justified by the use of a lowest observed adverse effect level, the shallow dose-response in the study and the absence of mechanistic information. The agreed **acceptable operator exposure level** (AOEL) was **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 agreed **acute reference dose** (ARfD) was **0.015 mg/kg bw** based on the 4-week rat study and applying a safety factor of 100.

The agreed dermal absorption values to be used in the risk assessment were 2.4% for the concentrate and 2% for the contaminated grain dust. The operator exposure estimate during the seed treatment was above the AOEL with the SeedTropex model, but realistic field studies showed an exposure level up to 21% of the AOEL. Similarly, the exposure estimate for the worker loading and sowing treated seed was above the AOEL with the SeedTropex model, but below the AOEL with a field study (26%).

As for the section of residues in food and feed, a radiolabel metabolism study was conducted on seed treated barley in the early 1980's. Due to the age of the study, and since at harvest maturity the total radioactive residues (TRR) in the grain and straw were less than 0.05 mg/kg, no identification of residues was attempted. The meeting of experts noted that the ADI for triazoxide is extremely low, and that the usual trigger values for identification that were applied in the study may not be applicable for very hazardous compounds. The experts had concerns that, despite the low level of radioactivity, triazoxide or metabolites with similar toxicological properties could be present, and identified a data gap for a new metabolism study in barley. In addition, the meeting on toxicology confirmed that not only triazoxide was of concern, but all its metabolites should be considered of comparable toxicity. On this basis, the initially proposed plant residue definition, triazoxide, is provisional only pending submission the further data to clarify the identity of plant residues. **No final residue definition for monitoring and risk assessment** could therefore be agreed.

In the acceptable evaluated residue trials data, all grain and straw samples were analysed for triazoxide, and in few trials for a metabolite, desoxy-triazoxide (M01). No residues were found above the LOQ (0.05 mg/kg). However, it was agreed that the analytical method used in these trials was **not validated at a sufficiently low LOQ to ensure that an exceedance of the ADI could be definitively excluded**. The meeting of experts noted, that the applicant indicated that new residue trials with a lower LOQ of 0.001 mg/kg have been recently conducted. However, these are not admissible for submission in the current process, and their relevance with regard to the (not yet defined) residue for risk assessment to be analysed for in residue trials, is unclear.

The available data are sufficient to address rotational crop residues for the model crops leafy and root crops, while residues in a third model crop (rotated cereal) could be conclusively addressed with the required new data for the primary cereal crop.

No data were submitted to study the nature and magnitude of residues in livestock. It was presumed in the rapporteur's assessment that residues in animal products are unlikely to occur, since triazoxide

levels in barley grain and straw were below the limit of quantification at harvest. However, as already stated, the LOQ of 0.05 mg/kg was considered by the experts not to be sufficiently low for risk assessment purposes. Taking into account the total residues in barley straw of 0.04 mg/kg in the radiolabel study, the maximum dietary livestock burden would be below the usual trigger value to require a livestock metabolism study. Nevertheless, given the very low ADI of triazoxide and the metabolites, the experts had concerns that transfer of toxicologically relevant residues from straw into livestock matrices may occur, even though at very low levels. It was concluded that livestock exposure to relevant residues and the potential of **carry over** of these **residues to food of animal origin** will have **to be further addressed** by the applicant. The decision, whether a livestock metabolism study should be required, would be dependant on the results of the identified data gap for a new plant metabolism study.

The chronic consumer risk assessment originally conducted by the RMS used default assumptions about residues in barley grain (only triazoxide present at LOQ level 0.05 mg/kg) and the WHO cluster diets to estimate the TMDI, and UK consumption data to estimate the UK NEDI. In both assessments intake estimates were below the ADI. With the same assumptions, but using consumption data from the EFSA PRAPeR model, without consideration of potential residues in food of animal origin, the **ADI was exceeded for one diet** (124%, Irish adult). When, in addition, residues in milk were assumed to be at LOQ level (0.01 mg/kg) in an indicative estimate to account for a potential carry-over of residues from straw in animal matrices, the ADI was exceeded for a number of national and regional diets in the EFSA PRAPeR model, in particular for children. In a provisional acute dietary risk assessment no exceedance of the ARfD of 0.015 mg/kg bw/day was observed.

However, **a robust consumer risk assessment cannot be conducted** at this stage due to the reasons outlined above.

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 d). Degradation of triazoxide proceeds either through reduction to desoxy-triazoxide (M01) or through production of triazoxide-amine (M02). Assessment based on the decline from the maximum observed indicates that M01 was moderate persistent in soil ($DissT_{50\ lab}$ = 32.4 – 56.7 d) and M02 could be considered high to very high persistent (decline M02 $DissT_{50\ field}$ = 239 – 447 d; excluding UK field trial where no decline is observed). A kinetic assessment of laboratory data allowed the applicant to derive kinetic half lives for M01 that are associated to a formation fraction of 1. 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. Photolysis slightly enhances degradation of triazoxide in soil, but it is not expected to contribute significantly to its environmental dissipation.

Field studies are available, some of them including measurements of the soil metabolites. Kinetic analysis of the field data presented by the applicant was discussed by the meeting of experts. The kinetic analysis was not fully accepted and the need of considering formation fractions of 1 for further modelling based on this analysis was agreed. Analysis of the data based on the decline of M02 has

been performed by the RMS, and the resulting half-lives (decline M02 $DissT_{50\ field}$ = 239 – 447 days; excluding UK field trial where no decline is observed) may be used in conjunction with the maximum observed of 18.7 % for exposure risk assessment. PECs soil presented in the DAR were calculated by the RMS for triazoxide and its soil major metabolites following standard procedures. Updated PECs soil with parameters agreed by the meeting of experts are reported in addendum 2 and do not result in a change of the risk assessment already performed.

According the available studies, triazoxide may be considered low to medium mobile in soil (K_{foc} = 245 – 1743 mL / g), M01 may be considered slightly mobile (K_{foc} = 2053 – 4148 mL / g), and (M02) may be considered low to medium mobile (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 proposed, further data could be needed if other uses at significant higher application rates are applied for in the future.

Triazoxide was stable to hydrolysis at pH 4, practically stable at pH 7, and readily hydrolyses at pH 9 (DT_{50} = 6.6 days). The main hydrolysis metabolite was triazoxide-oxone (M04). Triazoxide is rapidly photolysed in water (DT_{50} = 24.4 h equivalent to 3.5 natural solar days at 33 ºN). An additional study indicates that 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 triazoxide-desoxyamino (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 M01 in the water sediment systems. This kinetic analysis was only partially validated by the RMS (only whole system results for the Lienden system were confirmed). For the IJzendoorn system no reliable whole system half-lives for parent and 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 Lienden system.

Input parameters to be used for FOCUS PEC_{SW} were discussed and agreed in the meeting of experts. After the meeting, the RMS has presented an addendum with new FOCUS SW (Step 1 and Step 2) for metabolite M01 and M02 following the approach agreed by the meeting. However, the new PECs calculated do not alter the outcome of the risk assessment already presented by the RMS in the DAR.

Three different approaches based on FOCUS GW to calculate PEC GW were presented in the DAR. The meeting of experts agreed on the approach presented under B.8.6.d for the parent compound, but disagreed with the formation fractions assumed for metabolites M01 and M02, for which a formation fraction of 1 had to be used. After the meeting, the RMS presented a new groundwater assessment based on FOCUS PEARL v.3.3.3 and the input parameters agreed by the meeting of experts. Neither the parent, nor its major soil metabolites M01 and M02 exceeded the trigger of 0.1 µg /L, when the

EU representative use (cereals seed treatment, 6 g a.s. / ha) is simulated. However, due to the low ADI determined for this substance, 10% of the ADI would be reached for adults, toddlers and bottle fed infants, if residue levels of 0.05 µg/L, 0.017 µg/L and 0.011 µg/L, respectively, of each component (triazoxide, M01 and M02) were present in the water. These levels were not exceeded in any of the scenarios simulated for the representative use in cereal seeds. Nevertheless, reliability and predictive capacity of FOCUS GW models is expected to be lower in this low range of concentrations.
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 endpoint, 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 time scale. The conclusion was supported by an additional assessment for a fast feeding granivorous bird like the woodpigeon. In order to reach the $LD_{50,}$ woodpigeons would have to consume 2940 seeds (includes a 10-fold uncertainty factor). A long-term risk assessment on reproductive birds was considered relevant for the spring use of triazoxide as seed treatment (the autumn use may also be reproductively relevant for birds in some southern MSs). 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 spring use.
The tier 1 acute risk assessment for granivorous mammals was found to be low. Further refinements were required to identify a low long-term risk to granivorous mammals. Refinements were based on wood mouse as focal species and on use of measured residue data (see birds above), resulting in a TER value of 0.64. Further refinements were required to address the long-term risk to granivorous mammals. Risk assessment of secondary poisoning and consumption of contaminated drinking water was considered not relevant.
Triazoxide is proposed to be classified as very toxic to aquatic organisms. The acute risk to aquatic organisms was assessed to be low. Further refinements were required to address the long-term risk to fish. The risk to sediment-dwellers from the metabolite M01, M02 and M05 was assessed as low.
The acute risk to earthworms was considered to be low. The long-term risk to earthworms needs further refinements to fully address the potential toxicity of residues in the soil matrix. For other soil

non-target macro-organisms, the risk to springtails was low for all potential soil residues, but it still remains open to address the potential risk to soil litter degrading processes from triazoxide and the soil metabolites M01 and M02.
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 / 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 into new EU level endpoints.
- Use of standard protective equipment (trousers, work jacket, gloves) by the operators treating seed in order to have an exposure level below the AOEL (see point 2.12).

Critical areas of concern

- The available metabolism and residue data are not considered appropriate to conduct a robust consumer risk assessment due to the
    - uncertainty identified with regard to the nature of residues in plant commodities
    - uncertainty identified with regard to possible transfer of residues in animal products
    - need for a sufficiently low LOQ of the analytical method in studies on the magnitude of residues, to ensure that an exceedance of the ADI can be definitively excluded (which is currently not the case).
- The risk assessment of the formulation (containing triazoxide and tebuconazole) for the operator/worker/bystander and consumers could not be concluded and has to be considered at Member State level.
- The long-term risk assessment for granivorous birds needs further refinement.
- The long-term risk assessment for granivorous mammals needs further refinement.
- The long-term risk to fish needs to be addressed.
- The long-term risk to earthworms needs further refinements.

Appendix 1 – list of endpoints

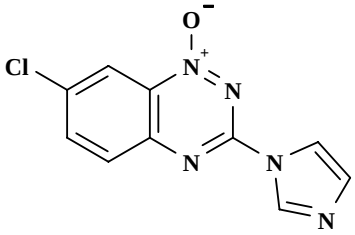
APPENDIX 1 – LIST OF ENDPOINTS FOR THE ACTIVE SUBSTANCE AND THE REPRESENTATIVE FORMULATION

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

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 ‡	Open
Identity of relevant impurities (of toxicological, ecotoxicological and/or environmental concern) in the active substance as manufactured	Toluene, max. 5 g/kg
Molecular formula ‡	$C_{10}H_6ClN_5O$
Molecular mass ‡	247.7 g/mol
Structural formula ‡	

Appendix 1 – list of endpoints

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 5.3g/l at 20°C (99%) acetonitrile 4.2g/l at 20°C (99%) dichloromethane 32g/l at 20°C (99%) dimethylformamide 20g/l at 20°C dimethylsulfoxide 14g/l at 20°C ethanol/PEG (1:1) 4.9g/l at 20°C hexane 0.05g/l at 20°C 1-octanol 2.3g/l at 20°C polyethylene glycol 4.1 g/l at 20°C 2-propanol 1.8g/l at 20°C toluene 6.9g/l at 20°C
Surface tension ‡	71.9mN/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 pHs 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%)

Appendix 1 – list of endpoints

Flammability ‡	Not considered highly flammable (99.1%)
Explosive properties ‡	Non-explosive (99.1%)
Oxidising properties ‡	Oxidising (99.1%)

Appendix 1 – list of endpoints

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)	Concentr. of a.s. (i)	Method kind (f-h)	Growth stage & season (j)	No. of applic. 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, others	F	barley leaf stripe, seed-borne net blotch, smuts	FS	20 g/L triazoxide, 20 g/L tebucona-ole	seed dressing	winter & spring	1	not applicable	not applicable	not applicable	2 - 3 (per/ha rate depends on seed rate; max. 6 g a.s./ha)	not applic.	Raxil S is a mixture with tebuconazole [1]

[1] No robust consumer risk assessment possible due to data gaps identified in section 3(Resideus), potential for exceedance of ADI in some exposure scenarios

* 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

Appendix 1 – list of endpoints

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 products 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 (provisional)
Food of animal origin		Open
Soil		Triazoxide (M01, M02)
Water	surface	Triazoxide
	drinking/ground	Triazoxide (based on the representative use)
Air		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 0.05 mg/kg.
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 water only) and the resulting extracts clean up on XTR-cartridges and the resulting eluants analysed by HPLC-MS/MS. The limit of determination was 0.05 mg/kg (milk 0.01 mg/l).

Appendix 1 – list of endpoints

Soil (analytical technique and LOQ)	Triazoxide (and its metabolites desoxy-triazoxide and triazoxide-amine) 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 metabolites desoxy-triazoxide) 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. Method with LOQ of 0.01 µg/l is required.
Air (analytical technique and LOQ)	Method with LOQ of 0.6 µg/m³ 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)

Appendix 1 – list of endpoints

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 absorbed within 24 hours (max plasma concentrations at 20-90 minutes) based on urine and bile. Only 50% considered available to the target tissues.
Distribution ‡	Widespread with the highest levels in liver, kidney, brown and peri-renal fat, adrenal and thyroid glands and nasal mucosa.
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 at least 87% of the dose eliminated within 24 hours.
Metabolism in animals ‡	Mainly by dechlorination, hydroxylation, de-oxidation, removal of the imidazole ring and conjugation; minimal cleavage of the benzotriazine ring structure.
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)	

Appendix 1 – list of endpoints

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/d (3-month rat) 0.4 mg/kg bw/d (1-year dog)	R48[19]
Relevant dermal NOAEL ‡	35 mg/kg bw/d (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 ‡	Red blood system (increased reticulocytes and RBC inclusions) and spleen (darkly coloured and increased weight).	
Relevant NOAEL ‡	0.05 mg/kg bw/d (LOAEL, 2 year rat) 0.3 mg/kg bw/d (NOAEL, 21 month mouse)	
Carcinogenicity ‡	No carcinogenic potential up to the highest dose tested (25 ppm)	

[19] R48/22 or R48/25 to be decided by EChA

Appendix 1 – list of endpoints

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction toxicity

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

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)	
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)

The notifier has stated that no human poisoning incidents are known to them and no detrimental health effects or long-term damage has been observed among employees.

Appendix 1 – list of endpoints

Summary (Annex IIA, point 5.10)	Value	Study	Safety factor
ADI ‡	0.00005 mg/kg bw/d	2-yr rat	1000
AOEL ‡	0.001 mg/kg bw/d	90-d rat, supported by the multigeneration	overall 200 (100 + correction for 50% bioavailability)
ARfD ‡	0.015 mg/kg bw	28-day rat	100

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 use of coverall in the model and single layer of clothing 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 sowing treated seed (26% of AOEL).	

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

RMS/peer review proposal

Appendix 1 – list of endpoints

Substance classified (name)	Toxic by inhalation and if swallowed (T,R23/25) Danger of serious damage to health by prolonged exposure through inhalation and if swallowed (R48/23/22 or 25[20]) May cause harm to breastfed babies (R64)

[20] R48/22 or R48/25 to be decided by EChA

Appendix 1 – list of endpoints

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 were submitted.
Residue pattern in processed commodities similar to residue pattern in raw commodities?	Not applicable.
Plant residue definition for monitoring	Triazoxide by default, however the residue definition is only **provisional** and a further plant metabolism study has been requested to further characterise the residue, due to the very low ADI set for triazoxide.
Plant residue definition for risk assessment	Triazoxide by default (no identification in the plant metabolism studies because of low levels of total [^{14}C] residues in the crops at harvest [<0.05 mg/kg]). However the residue definition is only **provisional** and a further plant metabolism study has been requested to further characterise the residue, due to the very low ADI set for triazoxide and the fact that all potential metabolites should be considered as of comparable toxicity.
Conversion factor (monitoring to risk assessment)	**open** – pending finalisation of the residue definitions

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

Animals covered	No data were submitted as positive residues in animal products were considered unlikely to occur due to low residues in barley grain and straw at harvest. A study may be required, depending on the results of the further plant metabolism study, due to the very low ADI set for triazoxide. –**open**
Time needed to reach a plateau concentration in milk and eggs	Not applicable –no study available.
Animal residue definition for monitoring	Residues definition for animals was not proposed as positive residues were not expected in animal products. Position may change depending on the results of the further plant metabolism study **-open**

Appendix 1 – list of endpoints

Animal residue definition for risk assessment	Residues definition for animals was not proposed as positive residues were not expected in animal products. Position may change depending on the results of the further plant metabolism study -**open**
Conversion factor (monitoring to risk assessment)	**open** – pending further assessment on whether animal residue definition is required
Metabolism in rat and ruminant similar (yes/no)	Not applicable –no ruminant study available.
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 with the exception of straw from rotated cereals.

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

Barley	Residues of triazoxide are stable for up to 24 months (during freezer storage) in barley forage, barley straw and barley grain.

Appendix 1 – list of endpoints

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)	0.1 mg/kg feed trigger may not be applicable due to very low ADI set for triazoxide; pending further assessment on livestock exposure when further plant metabolism study is available	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)	0.01 mg/kg trigger may not be applicable due to very low ADI set for triazoxide	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		-	

Appendix 1 – list of endpoints

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

Crop	Northern or Mediterranean Region, field or glasshouse, and any other useful information	Trials results relevant to the representative uses (a)	Recommendation/ comments	MRL estimated from trials according to the representative use	HR (c)	STMR (b)
Barley	Northern Field	14 x <0.05 mg/kg (grain) 14 x <0.05 mg/kg (straw)	Standard Approval Further residue trials have been requested with a lower LOQ, due to the very low ADI set for triazoxide. Studies should analyse for the residue definition for risk assessment – depending on the results of the further plant metabolism study.	0.05 mg/kg	0.05 mg/kg	0.05 mg/kg

(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

Appendix 1 – list of endpoints

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

ADI (mg/Kg bw/d)	0.00005
TMDI (% ADI) according to WHO European diet	**provisional** - pending finalisation of residue definition for risk assessment and availability of suitable occurrence data 80%, food of animal origin not taken into account
TMDI (% ADI) according to national diets	**provisional** - pending finalisation of residue definition for risk assessment and availability of suitable occurrence data UK: Less than 90% EFSA PRAPeR model: 124% (IE), all others were less than 82%, food of animal origin not taken into account When in addition intake from milk is considered at the default level/ LOQ level of 0.01 mg/kg to account for a potential carry-over of residues from straw, the ADI will be exceeded for a number of European diets (FR, UK, NL, DK, ES, SE, F, WHO EU regional diet and cluster diet D; highest 793% French toddler)
IEDI (WHO European Diet) (% ADI)	Not assessed.
NEDI (% ADI)	The same as TMDI (see above), since assessment was based on LOQ of 0.05 mg/kg in grain
Factors included in IEDI and NEDI	None
ARfD (mg/Kg bw/d)	0.015
IESTI (% ARfD)	Not assessed.
NESTI (% ARfD) according to national (to be specified) large portion consumption data	**provisional** - pending finalisation of residue definition for risk assessment and availability of suitable occurrence data UK: Less than 2% EFSA PRAPeR model: Less than 3% for all diets
Factors included in IESTI and NESTI	none

Appendix 1 – list of endpoints

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.	-	-	-	-

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

Barley (mg/kg)	0.05* mg/kg, **Provisionally** proposed as further residue trials are required, analysing the samples for the residue definition resulting from the requested plant metabolism study.

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

Appendix 1 – list of endpoints

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)	**Triazoxide-desoxy (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 140 d (Italian trial, molar basis). **Triazoxide-amino (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 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 ~~36 d~~ 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 90d, (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)	**Triazoxide-desoxy (M01) –** Max. 25.5 %AR after 155 d (125 d after flooding, end of study)

Appendix 1 – list of endpoints

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	X[21]	pH	t. °C / % MWHC	DT_{50} (d) First order bi-phasic: [a] 1st phase [b] 2nd phase	DT_{50} (d) overall	St. (r^2)	Method of calculation
Höfchen am Hohenseh Silt	n.a.	7.6	20°C /45%	[a] 33.3 [b] 498	258	0.99	bi-phasic,
Laacher Hof AIII Silt loam	n.a.	7.4	20°C /45%	[a] 7.1 [b] 412	278	0.99	
BBA 2.1 Sand	n.a.	5.9	20°C /45%	[a] 26.5 [b] 370	259	0.93	
Laacher Hof AXXa Sandy loam	n.a.	7.2	20°C /45%	[a] 9.2 [b] 404	208	0.99	
Geometric mean/median				[a] 15.5 [b] 419	250		

[21] X This column is reserved for any other property that is considered to have a particular impact on the degradation rate.

Appendix 1 – list of endpoints

Triazoxide-desoxy (M01)	Aerobic conditions							
Soil type	X[1]	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	n.a.	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**	(a) transformation rate: bi-phasic, (f.f. = 1) *(b) decline rate: non-linear regression analysis of data from the peak (n=3)* * poor fit, not included in mean, not considered reliable for risk assessment. **to be used for PEC soiland PEC SW/SED calculations together with a maximum formation observed of 17.7 %..
Laacher Hof AIII Silt loam	n.a.	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	n.a.	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	n.a.	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 ~~(c)~~– 145*		7.2 (d)		(d) mean value to be used in PECgw calculations together with a f.f. = 1.

Appendix 1 – list of endpoints

Field studies ‡

Parent	Aerobic conditions								
Soil type (application to bare soil, subsequently incorporated and cropped).	Location (country or USA state).	X[1]	pH	Depth (cm)	DT_{50} (d) actual	DT_{90}(d) actual	St. (r^2)	DT_{50} (d) Norm.	Method of calculation
Sandy loam	UK	n.a.	8.4	0-30	48	640	0.933	108.4	Time-step normalised to 20ºC and pF2. 2nd phase dissipation DT_{50} only used. (B.8.1.3.c.) DT_{50} = 325d derived from worst case DT_{90} = 1080 d, to be used for PEC soil calculation.
Silt loam	Germany	n.a.	7.4	0-30	99	851	0.930	102.2	
Silt loam	S. France	n.a.	8.7	0-30	18	705	0.951	98	
Silt loam	Italy	n.a.	8.2	0-30	29	1080	0.915	127.0	
Geometric mean/median					40	802		108	

Triazoxide-amino (M02)	Aerobic conditions								
Soil type	Location	X[1]	pH	Depth (cm)	DT_{50} (d) actual[#]	DT_{90} (d) actual	St. (r^2) actual / norm	DT_{50} (d) Norm.	Method of calculation
Sandy loam	UK	n.a.	8.4	0-30	no reliable	n.c.	0.946	213.4[**]	Actual: SFO decline after the max. observed.
Silt loam	Germany	n.a.	7.4	0-30	239	n.c.	0.95 / 0.98	28.6	
Silt loam	S. France	n.a.	8.7	0-30	313	n.c.	0.759 / 0.753	26.5	

Appendix 1 – list of endpoints

Triazoxide-amino (M02)	Aerobic conditions								
Soil type	Location	X[1]	pH	Depth (cm)	DT_{50} (d) actual[#]	DT_{90} (d) actual	St. (r^2) actual / norm	DT_{50} (d) Norm.	Method of calculation
Silt loam	Italy	n.a.	8.2	0-30	447 d	n.c.	0.698/ 0.813	38.2	Normalized: EXCEL (Solver) formation and degradation HS-SFO normalised to 20°C/ 100% FC (B.8.1.3.c) mean f.f.= 0.193 (uncertain). *For GWmodelling a f.f. = 1 to be used together with norm. geomean DT50 ** used for PEC soil calculation together with a maximum observed = 18.7 %. *** to be used for $PEC_{SW/SED}$ calculation together with a maximum observed = 18.7 %.
Geometric mean/median					322[***]			49.9[*]	

Appendix 1 – list of endpoints

n.a = not applicable n.c. = not calculated # Calculated by the RMS as decline after the maximum observed.

pH dependence ‡ (yes / no) (if yes type of dependence)	Triazoxide, triazoxide-desoxy (M01) and triazoxide-amino (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/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 DT50 of 325.3 d, soil density 1.5 g/cm3). Triazoxide desoxy (M01): Not required as laboratory DT90 values for triazoxide-desoxy (M01) <1 year. Instead a maximum PECsoil was based on what would be formed from accumulated parent residues i.e. 12.8% of 0.0148 mg/kg (corrected for molecular weight) = 0.00189 mg/kg x 0.932 = 0.00176 mg/kg. Triazoxide-amino (M02): Peak plateau concentration of 0.002154 mg/kg reached after 7 years. (Steady state concentration 06.58E-04 mg/kg). Assuming max. formation 18.7 % applied (mass basis) of application rate 6 g a.s/ha = 1.122 g/ha (worst case normalised field DT50 of 213.4 d, 5 cm soil depth and soil density 1.5 g/cm^3).

Laboratory studies ‡

Parent	Anaerobic conditions						
Soil type	X [22]	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	n.a.	7.6	20°C / 45%	137.1/ 455.5 (anaerobic phase only)	n.a.	0.96	SFO (non-linear regression)
Geometric mean/median				n.a.			

[22] X This column is reserved for any other property that is considered to have a particular impact on the degradation rate.

Appendix 1 – list of endpoints

Triazoxide-desoxy (M01)	Anaerobic conditions							
Soil type	X[1]	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	n.a.	7.6	20°C / 45%	n.c.	25.5*	n.a.	n.a	n.a.
Geometric mean/median								

n.a. not applicable. n.c. not calculated. *Maximum amount of triazoxide-desoxy 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/median						**673**	**0.7715**
pH dependence, Yes or No			No				

Triazoxide-desoxy (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/median						**2924**	**0.7337**
pH dependence (yes or no)			No				

Appendix 1 – list of endpoints

Triazoxide-amino (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/median						**979**	**0.7680**
pH dependence (yes or no)			Narrow range of soil pH tested (6-6.4). Triazoxide-amino (M02) is a base so 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, to be acceptable.				

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.

Appendix 1 – list of endpoints

PEC (soil) (Annex IIIA, point 9.1.3)

Parent	DT_{50} (d): 325.3 days
Method of calculation	Kinetics: pseudo first order Field or Lab: worst case DT90 from the field dissipation trial (Italy, Peters, B. 2005, B.8.1.3.b) of 1080 days (before normalisation) divided by 3.32
Application data	Crop: barley seed Depth of soil layer: 5cm Soil bulk density: 1.5g/cm^3 % plant interception: Seed treatment so no crop interception. Number of applications: 1 Interval (d): n.a. Application rate(s): 6 g as/ha (3 g a.s./100kg 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 yr			

Appendix 1 – list of endpoints

Triazoxide-desoxy (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 DT50 (3/4 soils with acceptable fit), calculated from peak amount with non-linear regression analysis.
Application data	Application rate assumed: 6 g as/ha corrected for molecular weight is 5.592 g/ha, then corrected to 0.715 g /ha assuming triazoxide-desoxy 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	0.00142		n.a.	
Short term 24h	0.00140	0.00141	n.a.	n.a.
2d	0.00138	0.00140	n.a.	n.a.
4d	0.00135	0.00138	n.a.	n.a.
Long term 7d	0.00119	0.00136	n.a.	n.a.
28d	0.00101	0.00120	n.a.	n.a.
50d	0.00077	0.00106	n.a.	n.a.
100d	0.00042	0.00082	n.a.	n.a.

Plateau concentration	Not required as DT90 values for triazoxide-desoxy (M01) <1 year. Therefore, a maximum PEC_{soil} of M01 formed from the accumulated parent residues has been calculated. i.e. 12.8% of 0.0148 mg/kg corrected for molecular weight x 0.932 = 1.76E-03 mg/kg. *(Simple first tier calculation assuming 17.7% applied and DT50 of 56.7 d gave peak plateau concentration of 1.43E-03 mg/kg reached in year 3 with steady state concentration 1.7E-05 mg/kg).*

Appendix 1 – list of endpoints

Triazoxide-amino (M02) Method of calculation	Molecular weight relative to the parent: No correction required. Maximum amount of metabolite formed is based on mass. DT_{50} (d): 213days Kinetics: SFO Field or Lab: Worst case DT50 from normalised field data.
Application data	Application rate assumed: 6 g as/ha corrected to 1.122 g/ha assuming triazoxide-amino is formed at a maximum of 18.7% of the applied dose. (No correction for molecular weight required).

$PEC_{(s)}$ (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial	0.001496		n.a.	
Short term 24h	0.001493	0.001494	n.a.	n.a.
2d	0.001489	0.001493	n.a.	n.a.
4d	0.001473	0.001489	n.a.	n.a.
Long term 7d	0.001473	0.001484	n.a.	n.a.
28d	0.001406	0.001451	n.a.	n.a.
50d	0.001339	0.001416	n.a.	n.a.
100d	0.001199	0.001342	n.a.	n.a.
Plateau concentration	First tier calculation assuming 18.7% applied and a DT50 of 313 days gave a peak plateau concentration of 2.698E-03 mg/kg reached in year 10, (with steady state concentration 1.202E-03 mg/kg).			

Appendix 1 – list of endpoints

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 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 Triazoxide-oxone (M04): 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). Triazoxide-desoxyamino (M05): max. 49.2% AR (60 hours, study end).
Quantum yield of direct phototransformation in water at Σ > 290 nm	Triazoxide: $\Phi = 2 \times 10^{-5}$ Triazoxide-desoxyamino (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 (eg 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	1.9/ 6.3*	0.498	0.1/ 0.3*	0.498	n.c.		SFO Excel Solver
Lienden	7.98-8.91	n.r.	22±2	4.3 /14.2	0.866	0.2/ 0.7*	0.866	n.c.		
Geometric mean/median				n.a.		n.a.				

* Values found unreliable by the RMS and the peer review, not to be used for risk assessment n.a. not applicable.

Appendix 1 – list of endpoints

Triazoxide-desoxy (M01)	Distribution (eg 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	281*	0.498	n.c.		n.c.		SFO Excel Solver
Lienden	7.98-8.91	n.r.	22±2	323	0.866	n.c.		n.c.		
Geometric mean/median			22±2	n.a.		n.c.		n.c.		

Triazoxide-desoxyamino (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*). * HPLC analysis gave higher results than TLC analysis for 'Lienden' system at days 15 and 30, of 12.5% and 13.4% applied after 30 days. HPLC analysis gave higher results than TLC analysis for 'Ijzendoorn' system at days 0-60 with a max. of 9.7% applied after 30 days.

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 * Values found unreliable by the RMS and the peer review, not to be used for risk assessment

Appendix 1 – list of endpoints

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 Kf_{OC} (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 108.4 d, (normalised, geometric mean of slower dissipation phase. Modelling refined to include worst case incorporation depth of 2.5 cm and additional metabolites).
Parameters used in FOCUSsw step 3 (if performed)	Version control no.'s of FOCUS software: v1.1 Vapour pressure: 1E-07 Pa at 20°C Kom/Koc: 673 mg/L 1/n: 0.771
Application rate	Crop: winter cereal seed treatment Crop interception: none, seed treatment Number of applications: 1 Application rate(s): 6 g as/ha Application window: October- February

Appendix 1 – list of endpoints

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
	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	0.5137		3.4575	
	24 h	0.4373	0.4755	2.9428	3.2001
	2 d	0.3722	0.4401	2.5047	2.9619
	4 d	0.2696	0.3795	1.8144	2.5538
	7 d	0.1662	0.3086	1.1187	2.0772
	14 d	0.0538	0.2043	0.3620	1.3746
	21 d	0.0174	0.1469	0.1171	0.9889
	28 d	0.0056	0.1128	0.0379	0.7593
	42 d	0.0006	0.0760	0.0040	0.5112

Appendix 1 – list of endpoints

FOCUS STEP 2 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Southern EU*	0 h	0.4178		2.8120	
	24 h	0.3556	0.3867	2.3934	2.6027
	2 d	0.3027	0.3579	2.0371	2.4090
	4 d	0.2193	0.3086	1.4757	2.0770
	7 d	0.1352	0.2510	0.9099	1.6894
	14 d	0.0437	0.1661	0.2944	1.1180
	21 d	0.0142	0.1195	0.0953	0.8043
	28 d	0.0046	0.0918	0.0308	0.6175
	42 d	0.0005	0.0618	0.0032	0.4158

*PECsw/sed values for triazoxide (S.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 DT50 more worst case & higher N.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	< 0.001	< 0.001	< 0.001	< 0.001
D1 (Lanna)	stream	< 0.001	< 0.001	< 0.001	< 0.001
D2 (Brimstone)	ditch	< 0.001	-	< 0.001	-
D2 (Brimstone)	stream	< 0.001	-	< 0.001	-
D3 (Vredepeel)	ditch	< 0.001	< 0.001	< 0.001	< 0.001
D4 (Skousbo)	pond	< 0.001	< 0.001	< 0.001	< 0.001
D4 (Skousbo)	stream	< 0.001	< 0.001	< 0.001	< 0.001
D5 (La Jailliere)	pond	< 0.001	< 0.001	< 0.001	< 0.001
D5 (La Jailliere)	stream	< 0.001	< 0.001	< 0.001	< 0.001
D6 (Thiva)	ditch	< 0.001	-	< 0.001	-
R1 (Weiherbach)	pond	< 0.001	-	< 0.001	-
R1 (Weiherbach)	stream	< 0.001	-	< 0.001	-
R3 (Bologna)	stream	< 0.001	-	< 0.001	-
R4 (Roujan)	Stream	< 0.001	< 0.001	< 0.001	< 0.001

Appendix 1 – list of endpoints

Metabolite Triazoxide-desoxy (M01) Parameters used in FOCUSsw step 1 and 2	Molecular weight: 231.6 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) DT50 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)	**STEP 3 NOT PERFORMED**.
Application rate	Crop: winter cereal seed treatment Number of applications: 1 Interval (d): n/a Application rate(s): 6 g as/ha Depth of water body: 30 cm Application window: October- February
Main routes of entry	Run-off + drainage. No spray drift assumed.

Appendix 1 – list of endpoints

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	0 h	0.0322	-	0.9407	
	24 h	0.0321	0.0321	0.9387	0.9397
	2 d	0.0320	0.0321	0.9367	0.9387
	4 d	0.0319	0.0320	0.9327	0.9367
	7 d	0.0317	0.0319	0.9267	0.9337
	14 d	0.0312	0.0317	0.9129	0.9267
	21 d	0.0308	0.0315	0.8992	0.9198
	28 d	0.0303	0.0312	0.8858	0.9130
	42 d	0.0294	0.0308	0.8596	0.8995

Appendix 1 – list of endpoints

FOCUS STEP 2 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Southern EU	0 h	0.0257		0.7526	
	24 h	0.0257	0.0257	0.7509	0.7517
	2 d	0.0256	0.0257	0.7493	0.7509
	4 d	0.0255	0.0256	0.7461	0.7493
	7 d	0.0254	0.0255	0.7413	0.7469
	14 d	0.0250	0.0254	0.7303	0.7414
	21 d	0.0246	0.0252	0.7194	0.7359
	28 d	0.0242	0.0250	0.7087	0.7304
	42 d	0.0235	0.0246	0.6877	0.7196
FOCUS STEP 3	NOT PERFORMED				

Metabolite Triazoxide-amino (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): 49.9 days (Normalised Field DT50, geometric mean. In accordance with FOCUS SFO) DT50 water/sediment system (d): triazoxide-amino (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)	**STEP 3 NOT PERFORMED**.

Appendix 1 – list of endpoints

Application rate	Crop: winter cereal seed treatment Number of applications: 1 Interval (d): n/a Application rate(s): 6 g as/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	0 h	0.0638	-	0.6247	---
	24 h	0.0638	0.0638	0.6245	0.6247
	2 d	0.0637	0.0638	0.6240	0.6245
	4 d	0.0636	0.0637	0.6232	0.6240
	7 d	0.0635	0.0637	0.6219	0.6234
	14 d	0.0632	0.0635	0.6189	0.6219
	21 d	0.0629	0.0634	0.6159	0.6204
	28 d	0.0626	0.0632	0.6129	0.6189
	42 d	0.0620	0.0629	0.6070	0.6159

Appendix 1 – list of endpoints

FOCUS STEP 2 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Southern EU	0 h	0.0511	-	0.4999	-
	24 h	0.0510	0.0510	0.4996	0.4998
	2 d	0.0510	0.0510	0.4992	0.4996
	4 d	0.0509	0.0510	0.4985	0.4992
	7 d	0.0508	0.0509	0.4975	0.4987
	14 d	0.0506	0.0508	0.4951	0.4975
	21 d	0.0503	0.0507	0.4927	0.4963
	28 d	0.0501	0.0507	0.4903	0.4951
	42 d	0.0496	0.0503	0.4856	0.4927

Metabolite Triazoxide-desoxyamino (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) DT50 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)	**STEP 3 NOT PERFORMED.**

Appendix 1 – list of endpoints

Application rate	Crop: winter cereal seed treatment Number of applications: 1 Interval (d): n/a Application rate(s): 6 g as/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	0 h	0.0003		0.0031	
	24 h	0.0003	0.0003	0.0031	0.0031
	2 d	0.0003	0.0003	0.0031	0.0031
	4 d	0.0003	0.0003	0.0031	0.0031
	7 d	0.0003	0.0003	0.0031	0.0031
	14 d	0.0003	0.0003	0.0031	0.0031
	21 d	0.0003	0.0003	0.0030	0.0031
	28 d	0.0003	0.0003	0.0030	0.0031
	42 d	0.0003	0.0003	0.0030	0.0030

Appendix 1 – list of endpoints

FOCUS STEP 2 Scenario	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Southern EU	0 h	0.0003		0.0025	
	24 h	0.0003	0.0003	0.0025	0.0025
	2 d	0.0003	0.0003	0.0025	0.0025
	4 d	0.0003	0.0003	0.0025	0.0025
	7 d	0.0003	0.0003	0.0025	0.0025
	14 d	0.0002	0.0003	0.0024	0.0025
	21 d	0.0002	0.0003	0.0024	0.0025
	28 d	0.0002	0.0002	0.0024	0.0024
	42 d	0.0002	0.0002	0.0024	0.0024

Appendix 1 – list of endpoints

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: PEARLv.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 field DT_{50}, normalised, (2^{nd} slower phase of dissipation only) of 108.4 d. K_{OC}: parent, arithmetic mean, 673 mg/l, $^1/_n$= 0.771. **Metabolites:** **Triazoxide-desoxy (M01):** Geometric mean parent DT50 lab 7.2 d (normalisation to 10kPa or pF2, 20 °C with Q10 of 2.2). K_{OC}: arithmetic mean, 2924 mg/l, $^1/_n$= 0.734. Formation fraction: 1.0 **Triazoxide-amino (M02):** K_{OC}: arithmetic mean, 979 mg/l, $^1/_n$= 0.768. Geometric mean parent DT50 field normalised 49.9 d. Formation fraction: 1.0 No field leaching or lysimeter studies submitted.
Application rate	Application rate: 6 g/ha. No. of applications: 1 Time of application (month or season):

Appendix 1 – list of endpoints

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

	Scenario	Parent (µg/L)	Triazoxide-desoxy (M01)	Triazoxide-amino (M02)
FOCUS PEARL / Winter cereals	Chateaudun	<0.001	<0.001	<0.001
	Hamburg	<0.001	<0.001	<0.001
	Jokioinen	<0.001	<0.001	<0.001
	Kremsmunster	<0.001	<0.001	<0.001
	Okehampton	<0.001	<0.001	<0.001
	Piacenza	<0.001	<0.001	<0.001
	Porto	<0.001	<0.001	<0.001
	Sevilla	<0.001	<0.001	<0.001
	Thiva	<0.001	<0.001	<0.001

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

Appendix 1 – list of endpoints

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	e.g. negligible

Residues requiring further assessment

Environmental occurring metabolite requiring further assessment by other disciplines (toxicology and ecotoxicology).	Soil: triazoxide + triazoxide-desoxy (M01) + triazoxide-amino (M02). Surface water: triazoxide Sediment: triazoxide + triazoxide-desoxy (M01) and triazoxide-desoxyamino (M05) + triazoxide-amino (M02). Ground water triazoxide + triazoxide-desoxy (M01) + triazoxide-amino (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

Appendix 1 – list of endpoints

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

Candidate for R53

Appendix 1 – list of endpoints

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 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) measured dissipation of triazoxide from treated barley seed placed onto soil surface giving a 10-day ftwa of 0.46 Published data (Prosser revised 2001) indicates that birds can consume seeds in artificial spill situations. Data for small birds indicate a level of concern, data for fast-eating birds helps to demonstrate a degree of safety. Radio tracking of woodpigeon in arable areas used to refine PT of 0.24 for this species (Wolf 2004)				

[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)

Crop and application rate: 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[3]
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]	5

Appendix 1 – list of endpoints

Indicator species/Category[2]	Time scale	ETE	TER	Annex VI Trigger[3]
Higher tier refinement (Birds)				
	Acute	9.9[3]	**9.1**[4]	10
	Long-term	11.4	**2.2**[5]	5
Tier 1 (Mammals)				
Granivorous	Acute	6.9	14.2	10
Granivorous	Long-term	6.9	**0.3**[2]	5
Higher tier refinement (Mammals)				
	Long-term	3.17	**0.64**[6]	5

[1] based on SANCO 4145 first tier assumption for a small generic 15 g bird,
[2] only relevant for spring use for which further refinement is required. Autumn use considered to be outside of main reproductive period, particularly for northern MS.
[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 41445 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 (490g woodpigeon) is 2940 (this includes a 10 fold uncertainty factor).
[5] Standard 15 g granivorous bird. Refinement of dose of triazoxide on seed using 10-d ftwa of 0.46. Further refinement required to support spring use at MS level
[6] Standard granivorous mammal. Refinement of dose of triazoxide on seed using 10-d ftwa of 0.46. Further refinement required to support spring use at MS level.

Appendix 1 – list of endpoints

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	a.s.	28 d (static)	Growth NOEC	NA
No formulation study presented[1]	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[1]	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

Appendix 1 – list of endpoints

Group	Test substance	Time-scale (Test type)	End point	Toxicity[1] (mg/L)
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[1]	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
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 PRAPeR 48 concluded that that an additional chronic study was needed for fish. The chronic fish study should also address the potential for endocrine effects.

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

FOCUS Step 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 or mg/kg sed)	TER	Annex VI Trigger[1]
a.s.	Fish	0.077	Acute	0.0005sw[1]	154	100
a.s.	Fish	NA	Chronic	0.0005sw[1]	NA	10
a.s.	Aquatic invertebrates	7.2	Acute	0.0005sw[1]	14400	100
a.s.	Aquatic invertebrates	NA	Chronic	0.0005sw[1]	NA	10

Appendix 1 – list of endpoints

Test substance	Organism	Toxicity end point (mg/L)	Time scale	PEC_i (mg/l or mg/kg sed)	TER	Annex VI Trigger[1]
a.s.	Algae	0.039 (biomass) 0.074 (growth rate)	Chronic	0.0005sw[1] 0.0005sw[1]	78 148	10
a.s.	Sediment-dwelling[2] organisms	NA	Chronic	0.0035sed[1]	NA	10
Metabolite M01	Sediment-dwelling organisms	10 mg M01/kg sed	Chronic	0.0009407sed[1]	10630	10

[1] PEC values represent worst case values for winter cereals in Northern EU)
[2] parent triazoxide is not expected to persist in the sediment phase therefore no risk assessment is performed.

Bioconcentration				
	Active substance	Metabolite M01	Metabolite M02	
$logP_{O/W}$	2.04	0.92	Not available	

[1] log $P_{O/W}$ <3 for parent triazoxide and M01 therefore no assessment required. No definitive log Pow 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	

Appendix 1 – list of endpoints

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

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

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] LR50 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'[4] – 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'[4] – 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'[4] – treated seeds ext. laboratory, Lufa 2.1 sand, 78 d corresponding to	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 1 and Annex VI is therefore applied
[4] 'Raxil S FS 040', containing 20 g/l triazoxide + 20 g/l tebuconazole, is the supported formulation

Appendix 1 – list of endpoints

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			
	Technical triazoxide	Acute 14 days	LC_{50} >500_{corr} mg a.s./kg d.w.soil[1]
	'Raxil S FS 040' mixed into test soil	Acute	14 d LC5O >1000 mg 'Raxil S FS 040'/kg d.w soil (>20 mg triazoxide)[5]
	'Raxil S FS 040' as treated seed	Chronic	NOEC 950 kg treated seed/ha
	Metabolite M01	Acute	LC_{50} >1000 mg /kg d.w.soil
	Metabolite M02	Acute	LC_{50} >500_{corr} mg /kg d.w.soil[1]
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	Triazoxide-desoxy (M01) mixed into OECD 207 artificial soil 28 d study	Chronic	LC50 >100[2] mg/kg dw soil NOEC 100 mg/kg dw soil
Folsomia candida	'Raxil S FS 040' mixed into OECD 207 artificial soil 28 d study	Chronic	LC50 > 2500 mg 'Raxil S FS 040'/kg dw soil[3] NOEC 2500 mg 'Raxil S FS 040'/kg dw soil

Appendix 1 – list of endpoints

Test organism	Test substance	Time scale	End point[1]
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
Field studies			
Reliability of existing litter bag study (Lechelt-Kunze, Chr., 2003) could not be assessed.			

[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 endpoint for 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 only2 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

Crop and application rate

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[2]	10
	Preparation	Chronic	200 kg seed/ha[3]	**4.75**[4]	5
	Metabolite M01	Acute	0.002 mg M01/kg d.w. soil[5]	>500000	10
	Metabolite M02	Acute	0.002 mg M02/kg d.w. soil	>250000	5

Appendix 1 – list of endpoints

Test organism	Test substance	Time scale	Soil PEC[2]	TER	Trigger
Other soil macro-organisms					
Collembola	Technical triazoxide.	Chronic	0.015 mg triazoxide /kg d.w. soil[1]	16666	5
	Raxil S FS 040	Chronic	0.015 mg triazoxide/kg d.w. soil[1]	1666[2]	5
	Metabolite M01	Chronic	0.002 mg M01/kg d.w. soil[5]	50000	5
Soil litter processes[6]					

[1] peak plateau concentration (steady state PECsoil accumulation + annual soil loading (Section B.8.3 (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 (new chronic studies with solo triazoxide formulation and MO1 are available but not assessed)
[3] maximum proposed drilling rate for treated seed
[4] calculated using a NOEC equivalent to a drilling rate of 950 kg treated seed/ha (maximum rate tested in study)
[5] based on the amount that would be expected to be formed from the accumulated parent residue (rounded up from actual value of 0.0017 mg given in Section B.8.3 (d))
[6] data to address the potential risk to soil litter processed from triazoxide and the soil metabolites M01 and M02 is required

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 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. Proposed use as a seed treatment effectively precludes exposure outside of the treated area therefore risk assessment not currently required under SANCO 10329.

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

Test type/organism	end point
Activated sludge	EC50 >10000 mg technical triazoxide/l

Appendix 1 – list of endpoints

Ecotoxicologically relevant compounds (to be confirmed)

Compartment	
soil	Triazoxide
water	Triazoxide
sediment	Metabolite M01
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 Toxic to aquatic organisms** **R53 May cause long term adverse effects in the aquatic environment** **'N' symbol**

[1] MS should confirm this at product authorisation using agreed Annex 1 tebuconazole toxicity endpoints and/or formulation toxicity data for 'Raxil S FS 040'.
2 based on Dir 2006/8/EC

APPENDIX 2 – ABBREVIATIONS USED IN THE LIST OF ENDPOINTS

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

Appendix 2 – abbreviations used in the list of endpoints

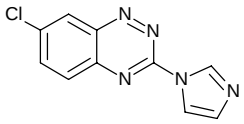
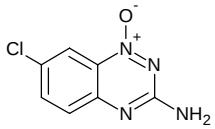
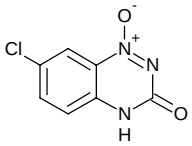
K_{oc}	organic carbon adsorption coefficient
K_{om}	organic matter adsorption coefficient
L	litre
LC	liquid chromatography
LC-MS	liquid chromatography-mass spectrometry
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LC_{50}	lethal concentration, median
LD_{50}	lethal dose, median; dosis letalis media
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification (determination)
µg	microgram
mN	milli-Newton
MRL	maximum residue limit or level
MS	mass spectrometry
NESTI	national estimated short term intake
NIR	near-infrared-(spectroscopy)
nm	nanometer
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
PD	proportion of different food types
PEC	predicted environmental concentration
PEC_A	predicted environmental concentration in air
PEC_S	predicted environmental concentration in soil
PEC_{SW}	predicted environmental concentration in surface water
PEC_{GW}	predicted environmental concentration in ground water
PHI	pre-harvest interval
pK_a	negative logarithm (to the base 10) of the dissociation constant
PPE	personal protective equipment
ppm	parts per million (10^{-6})
ppp	plant protection product
PT	proportion of diet obtained in the treated area
r^2	coefficient of determination
RPE	respiratory protective equipment
STMR	supervised trials median residue
TER	toxicity exposure ratio
TLC	thin-layer-chromatography

Appendix 2 – abbreviations used in the list of endpoints

TMDI	theoretical maximum daily intake
TRR	total radioactive residue
UDS	unscheduled DNA synthesis
UV	ultraviolet
WHO	World Health Organisation
yr	year

Appendix 3 – used compound code(s)

APPENDIX 3 – USED COMPOUND CODE(S)

Code/Trivial name	Chemical name	Structural formula
M01 desoxy-triazoxide	7-chloro-3-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