PEER REVIEW REPORT ON **TRIFLURALIN** 04.04.2005

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1. Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis

No.	Column 1 Data point based on draft assessment report or comments from MS	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (i) Co-rapporteur, and (ii) Rapporteur	Column 4 Data requirement or Open Point (if data point not addressed or fulfilled) (Annex point)
(i)	Vol. 1, 1.5.2 , Effects on harmful organisms	FI: In Volume 1 point 1.5.2, it is stated that " trifluralin is incorporated in soil to be protected from degradation by sunlight". However, in Vol 1 in point 2.5.2 route of photolytic degradation in soil, it is stated that "irradiation of trifluralin on a soil surface under artificial sunlight…..after 30 days the majority of the applied radioactivity was present as trifluralin". These statements are contradictory, and we suppose that the incorporation of trifluralin to soil is due to the volatility of the trifluralin.	(ii) We agree with this comment	
(ii)	Vol. 1, 2.1.4 (Classification and labelling), see also 2.1.2 (Physical and chemical properties)	DE: It is strongly recommended not to replace the safety phrase S 62 (in principle necessary because of R 65 labelling of the product) by S 46. (Justification: It should be clearly expressed not to induce vomiting before seeking medical advice. The term "immediately" (S 46) could be not sufficient in this context)	(ii) According to Dir.2001/59/EC (which has amended Dir.67/548/EEC) the safety phrase S62 ("If swallowed, do not induce vomiting: seek medical advice immediately and show this container or label") should be used for substances and preparations classified as harmful with R65, except when S45 or S46 are obligatory. That is why S62 was not included in the label. However, we agree with you that S62 is more appropriate than S46 ("If swallowed, seek medical advice immediately and show this container or label") and the DAR will be amended accordingly.	**RMS to revise the DAR.**

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(iii)	Vol. 3, B.2.1.1, Melting point Vol. 1, 4.2	UK: Agree with RMS, a new study using pure material is required. DAS: A new study on melting point was completed 30 July 2003 using high purity (99.4%) analytical grade active substance (DAS Report FAPC033079). (This report is now available and will be submitted on request)	(ii) DAS has recently submitted (November 2003) a new GLP study on melting point, using pure a.s. as test material. The test will be evaluated by the RMS and the evaluation will be included in an Addendum of the DAR.	RMS should evaluate the new study on melting point and include this evaluation in an Addendum of the DAR. (IIA 2.1.1) Evaluation Meeting (15.01.2004): **Open point:** **RMS to include the evaluation of the new study on melting point in an addendum.**
(iv)	Vol. 3, B.2.1.2/B.2.1.3, Boiling point and temperature of decomposition or sublimation	NL: test should be carried out with purified a.s. The change of colour (indicating decomposition) of the technical material can be caused by the impurities. UK: New data generated with pure a.s. are required, together with temperature at which decomposition occurs. The decomposition is attributed only by colour change which may be an impurity rather than active substance. A temperature should be provided	(ii) DAS has recently submitted (November 2003) a new GLP study on boiling/decomposition point, using pure a.s. as test material. The test will be evaluated by the RMS and the evaluation will be included in an Addendum of the DAR.	RMS should evaluate the new study on boiling/decomposition point and include this evaluation in an Addendum of the DAR. (IIA 2.1.2 & 2.1.3) Evaluation Meeting (15.01.2004): **Open point:** **RMS to include the evaluation of the new study on boiling/ decomposition point in an addendum.**

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(v)	Vol. 3, B.2.1.4, Density	UK: Agree with RMS new data would not yield additional information.	(ii) The data on relative density are considered adequate and no data gap is identified in level 4 of DAR.	-
(vi)	Vol. 3, B.2.1.5, Vapour pressure	UK: The DAR states the purity was 100%, is this correct?	(ii) Yes. In the Certificate of Analysis of the test material, the reported purity is 100%.	-
(vii)	Vol. 3, B.2.1.11, Spectra for impurities	UK: Are these data necessary i.e. is N-nitroso-di-n-propylamine a significant impurity? If it is then a new study is required because these data are published, very old and lack details e.g. purity of test substance	(ii) N-nitroso-di-n-propylamine is a relevant impurity, not a significant one (Its content level is max. 0.5mg/kg). Despite the deficiencies of the data submitted (which are highlighted in DAR) no new data were required in level 4 of DAR since N-nitroso-di-n-propylamine is a quite well known molecule and further data would not provide significant new information.	-
(vii)	Vol. 3, B2.1.12, Water solubility	NL: Is there an explanation for the difference of a factor 2 for the solubility between the two studies, as the purity difference is not that large.	(ii) No justification/explanation has been submitted, however, both results indicate that trifluralin is slightly soluble in water.	-
(ix)	Vol. 3, B.2.1.14, Partition coefficient	UK: Substance was 100% pure – this appears to be high. Agree a.s. is lipophilic.	(ii) We agree, however, in the Certificate of Analysis of the test material, the reported purity is 100%.	-
(x)	Vol. 3, B.2.1.15, Stability in water	UK: Agree with RMS new data would not yield additional information.	(ii) The data on hydrolysis are considered adequate and no data gap is identified in level 4 of the DAR.	-

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(xi)	Vol. 3, B.2.1.16, Stability in water	UK: Suggest this section be summarised for tabular presentation or cross refer to appropriate section in DAR	(ii) The result of our evaluation regarding the photochemical degradation of trifluralin in water should be presented in tabular format. However, we also believe that for reasons of transparency all the deficiencies of the study should be highlighted.	-
(xii)	Vol. 3, B.2.1.19, Stability in air	UK: Data suggest long range transport unlikely	(ii) We agree.	-
(xiii)	Vol. 3, B.2.1.20, Flammability	UK: Typographical error, statement should read "Trifluralin is a non-pyrophoric substance."	(ii) We agree with the editorial comment and the DAR will be amended accordingly.	**RMS to revise the DAR**
(xiv)	Vol. 3, B.2.2.5, Oxidising properties	UK: Is this a statement from the RMS or data submitter? Could the data submitter's statement be included together with the opinion of RMS.	(ii) It is the brief conclusion of the expert's assessment on the p.p.p.'s oxidising potential, which is acceptable. The actual assessment of the expert is much more detailed for each individual component of the p.p.p. Because of the extent and the tabular format of the data, it was not feasible to include the detailed assessment of the company's expert in the DAR.	-

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(xv)	Vol. 3, B.2.2.7, Flammability	UK: Would suggest to add '..for liquid' to indicate that this is not a data gap, but that the test is not appropriate for the formulation type.	(ii) We think that the standard phrase "not applicable" is used by definition when the respective test is considered not appropriate/relevant for the evaluation of the specific p.p.p. , not when a data gap is identified. Furthermore, it is widely known that the flammability test is not applied for liquids. The above standard phrase has been used in several cases in the table of phys/chem properties of the Treflan EC. Why an explanation/justification should be included only for flammability?	-
(xvi)	Vol. 3, B.2.2.11 & B.2.2.12, Viscosity	UK: New GLP data needed at 40ºC Data suggest that R65 is appropriate but data do not satisfy study requirements/conditions.	(ii) The kinematic viscosity of the p.p.p. was determined to be 2.53 mm^2/sec at 20 ^oC and therefore it is not expected to exceed the exemption criterion of 7 mm^2/sec at 40 ^oC. We agree that the test temperature was not the appropriate but we believe that a new test at 40 ^oC would not result in a different conclusion i.e. the R65 would still be required.	-
(xvi)	Vol. 3, B.2.2.13, Surface tension	UK: Data at 25ºC appropriate and suggests that R65 is appropriate. Surface tension data alone are not sufficient to positively classify with respect to R65, therefore viscosity data at 40ºC still required.	(ii) We agree that the surface tension data alone are not sufficient for R65 classification. See also our response on the viscosity comment (xvi).	-

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(xvii)	Vol. 3, B.2.2.16, Storage stability – emulsion stability	UK: Emulsion stability test suggests agitation of product in the spray tank required during mixing and loading and until spraying complete.	(ii) We agree that on the label a phrase suggesting that the product in the tank mix should be under stirring is appropriate.	-
(xviii)	Vol. 3, B.2.2.16, Low temperature stability	UK: Would suggest 'Protect from frost' to appear on the label. The study did not cycle the temperature.	(ii) The study did not cycle the temperature, however, the stability on low temperature of the p.p.p. was tested according to CIPAC MT 39.1, which is acceptable. Treflan EC complies for the low temperature stability test with FAO specification for trifluralin EC formulations (183/EC/S) i.e. max.0.3ml separated solid/ liquid. We agree that on the label a phrase suggesting that the product should be protected from frost is appropriate.	-

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(xix)	Vol. 3, B.2.2.17, Shelf life Vol. 1, 4.2	DAS: The 2-year storage study will be completed in April 2004. DAR comments regarding "UK ambient temperature" and shelf-life specifications were forwarded to the study's Sponsor Monitor for incorporation into the final report. UK: Would agitation address concerns as per 2.2.16 (emulsion stability) above	(ii) When finished, the 2-year storage stability test of formulation EF-1521 should be submitted. The study should include data on the content of impurity N-nitroso-di-n-propylamine (NDPA) in the p.p.p., before and after storage, in order to demostrate that the NDPA content of the p.p.p. does not exceed the respective FAO specified limits throughout the shelf-life period (IIIA 2.7) Regarding emulsion stability comment see (xvii)	Data requirement: When finished, the 2-year storage stability test of formulation EF-1521 should be submitted. The study should include data on the content of impurity N-nitroso-di-n-propylamine (NDPA) in the p.p.p., before and after storage, in order to demostrate that the NDPA content of the p.p.p. does not exceed the respective FAO specified limits throughout the shelf-life period (IIIA 2.7) Evaluation Meeting (15.01.2004): The Task Force can not provide data as expected. 2-year study will be submitted by the Task Force (in March/April). **Data requirement:** **Notifier to submit 2-year storage stability test of formulation EF-1521**

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(xx)	Vol. 3, B.2.2.17, Shelf life Vol. 1, 4.2	DAS: Data on the content of impurity NDPA after 2 years of storage will be reported in a study which is separate from the ongoing 2-year storage study. (Retained samples that are two years old have been analyzed for NDPA. The levels of NDPA will be documented and a report will be submitted showing the levels. This report will be available in October 2003 and will be submitted on request)	(ii)DAS has recently submitted (November 2003) a study (non-GLP) with data on the content of impurity NDPA in 4 batches of EF-1521 formulation, 2 years after manufactured. The study is separated from the on going 2-year storage study. The study will be evaluated by the RMS and the evaluation will be included in an Addendum of the DAR.	RMS should evaluate the new study with data on the content of one impurity in 4 batches of EF-1521 formulation, 2 years after manufactured and include this evaluation in an Addendum of the DAR. (IIIA 2.7) Evaluation Meeting (15.01.2004): Task force to submit data on one impurity regarding to shelf life. **Open point:** **RMS to include the evaluation of the new shelf life study in an addendum.**
(xxi)	Vol. 3, B.2.2.28, Emulsifiability	UK: Data suggest some separation of emulsion needing agitation on the label	(ii) see (xvii)	-

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(xxii)	Vol. 3, B.2.2.28 EAF-283	UK: What is 'Bloom', data submitter to define and qualify in terms of emulsion stability	(ii) The emulsion stability data refer to another formulation (EAF-283), which is similar to the lead formulation Treflan EF-1521. Although clarifications on the test results are necessary they were not asked since data on the emulsion stability of the actual lead formulation Treflan EC (EF-1521) were submitted. Our evaluation was based on the latter data (which refer to Treflan EC before and after accelerated storage test).	-
(xxiii)	Vol. 3, B.2.2.33	UK: Agree with data requirement for MS	(ii) Appropriate data on physical and chemical compatibility of Treflan EC with other products should be submitted at MS level if the p.p.p. is to be applied in tank-mixes.	Data requirement at Member State level: If the p.p.p. is to be applied in tank-mixes, appropriate data on physical and chemical compatibility of Treflan EC with other products should be submitted at MS level Evaluation Meeting (15.01.2004): Data requirement confirmed. **Data requirement:** **The procedures for cleaning equipment has to be adressed on MS level.**

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(xxiv)	Vol. 3, B.3.5.2, Procedures for cleaning application equipment	DAS: A new justification that a study to demonstrate the effectiveness of cleaning procedures has been prepared and includes new text to replace the original text for this Annex Point in the Summary Dossier. (The main source of the information provided in the Summary Dossier was an internal Dow AgroSciences Manufacturing guideline on cleaning bulk tank and returnable mini-bulks. It is now recognised that the information required to fulfil this Annex Point needs to be directed at cleaning of sprayer equipment and not to those procedures which may be available to a manufacturing site. The new justification and text is provided electronically to the RMS)	(ii)The applicant has submitted information to demonstrate the effectiveness of cleaning procedures. These data will be included in an Addendum of the DAR	The RMS should include information on the effectiveness of cleaning procedures in an addendum. Evaluation Meeting (15.01.2004): **Open point:** **RMS to include information on the effectiveness of cleaning procedures in an addendum.**
(xxv)	Vol. 3, B.3.5.4, Recommended methods and precautions concerning handling, storage, transport or fire of preparation Vol. 1, 4.3	DAS: Information on transportation (Road & Rail, Sea, and Air) of EF-1521 was omitted from the Summary Dossier in error but is provided in Section 14 of the Safety Data Sheet for the preparation. Specific recommendation is given that sample shipment is not allowed by mail. A copy of the Safety Data Sheet was also omitted from the full Dossier in error. (A copy of the Safety Data Sheet is provided electronically to the RMS)	(ii)The applicant has submitted the MSDS for the formulation. Data on information on transport (Road & Rail, Sea and Air) will be included in an Addendum of the DAR	The RMS should include the information on transport (Road & Rail, Sea and Air) in an addendum Evaluation Meeting (15.01.2004): **Open point:** **RMS to include the information on transport (Road & Rail, Sea and Air) in an addendum**

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(xxvi)	Vol. 3, B.5.1.2, Analytical methods for the determination of isomers, impurities, and additives in the active substance as manufactured Vol. 1, 2.2.1 Vol. 1, 4.5	NL: Method NAFST460 shows a not acceptable high recovery for impurity 1, and also the standard deviation is rather high. It looks very much so that there is another compound under impurity 1. Is there sufficient evidence that the selectivity is sufficient, e.g. from the calibration curve offset? UK: Conclusion states LOQ to be confirmed, does this mean that LOQ have not been supplied? DAS: The report for determination of significant impurities in trifluralin technical stated the "limit of determination was 0.05% w/w", which was based on the lowest concentration used in the linearity test and is not equivalent to LOQ. LOQ has been determined based on peak area in linearity test to be 0.01% w/w for impurities A, B, C, and D, 0.02% for impurity E, and 0.03% for impurity F. LOQ Calculation = [(SD/Mean)*10 (LOQ factor)] * [(1 µg/mL impurity standard)/(2000 µg/mL technical standard)]	(ii) Method NAFST460 (GC/ECD) is submitted for the determination of the significant impurities 1-6 in trifluralin technical. Selectivity of the method: It is a fact that one individual recovery value for impurity 1 is outside the acceptable limits (141%) and the %RSD value for this impurity at the fortification level 1.24%w/w is rather high (3.4%). However, the mean recovery for this impurity for the two fortification levels tested is within the acceptable limits. Additionally, since the identification of the impurities was performed by GC/MS analysis we have no reasons to suspect that there is another compound under impurity 1. Sensitivity of the method: According to the Guidance doc. SANCO/3030/99, rev. 4, LOQ is defined as the lowest concentration tested at which an acceptable mean recovery with an acceptable RSD is obtained. This in not the case for this method: although it is stated that LOQ=0.05% w/w, the lowest fortification level is 0.1% w/w for each impurity in the recovery experiment and in the range of 0.08-1.24% w/w in the precision experiment.	Data requirement: LOQ values for the method of analysis for impurities of trifluralin technical (Dow AgroSciences) should be confirmed. If the notifier insists on the LOQ of 0.05%, the method should be validated at concentrations as low as 0.05% w/w (in terms of precision and accuracy) otherwise the notifier has to supply a new, higher LOQ value for each impurity, which should be the lowest concentration tested at which an acceptable mean recovery with an acceptable RSD is obtained. (In every case the LOQ for each significant impurity should not be higher than the specified maximum content of this impurity in the technical). (IIA 4.1.2) Evaluation Meeting (15.01.2004): Task Force will submit a new argumentation on the LOQ values **Data requirement:** **Notifier to submit LOQ values for the method of analysis for impurities of trifluralin technical** Essential for unconditional Annex I inclusion. .

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(xxvii)	Vol. 3, B.5.1.3, Evaluation and assessment of methods for formulation analysis Vol. 1, 2.2.2 Vol. 1, 4.5	UK: Conclusion states surfactants have changed and that this is minor, if all surfactants have changed then this suggests that the formulation change is major. DAS: A method for the representative preparation, EF-1521, has been validated and includes linearity as well as precision and accuracy data (Protocol No. DAS-AM-03-021). (This report will be available in October 2003 and will be submitted on request)	(ii) DAS has recently submitted (November 2003) a GLP analytical method along with its validation data for the determination of the a.s. in the lead formulation, Treflan EF-1521. The method will be evaluated by the RMS and the evaluation will be included in an Addendum of the DAR.	The RMS should evaluate the new analytical method submitted for the determination of the a.s. in the lead formulation, Treflan EF-1521 and include this evaluation in an Addendum of the DAR (IIIA 5.1.1) Evaluation Meeting (15.01.2004): **Open point:** **RMS to include evaluation of new analytical method for the determination of the a.s. in the lead formulation in an addendum**

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(xxviii)	Vol. 3, B.5.1.3, Evaluation and assessment of methods for formulation analysis Vol. 1, 2.2.2 Vol. 1, 4.5	DAS: A method for determination of N-nitrosamines in the representative preparation, EF-1521, has been validated. (This report will be available in October 2003 and will be submitted on request)	(ii) DAS has recently submitted (November 2003) a GLP analytical method along with its validation data for the determination of the Di-n-propyl-nitrosoamine in the lead formulation, Treflan EF-1521. The method will be evaluated by the RMS and the evaluation will be included in an Addendum of the DAR.	The RMS should evaluate the new analytical method submitted for the determination of the Di-n-propyl-nitrosoamine in the lead formulation, Treflan EF-1521 and include this evaluation in an Addendum of the DAR (IIIA 5.1.2) Evaluation Meeting (15.01.2004): **Open point:** **RMS to include evaluation of the new analytical method for the determination of the Di-n-propyl-nitrosoamine in the lead formulation in an addendum.**
(xxix)	Vol. 3, B.5.2, Methods for plants	UK: ILV for study GRM 96.12 is required if method needed for monitoring. However, it is noted that crops are not proposed/not subject to MRLs at this time.	(ii) Method GRM 96.12 is not intended to be used for monitoring purposes at this stage, since there are other fully validated methods for the determination of trifluralin residues, covering all crops included in the list of intended uses. Therefore no ILV is required for this method. If alfalfa is included in the list of intended uses for MS authorization in the future, this data requirement can be dealt at MS level.	-

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(xxx)	Vol. 3, B.5.3, Methods for soil, water, air		(ii) If it is decided that the metabolite TR-4 is included in the residue definition for soil and the metabolites TR-6 and TR-15 are included in the residue definition for water, fully validated analytical methods determining these metabolites in soil and water respectively will be required.	Open point: If it is decided that the metabolite TR-4 is included in the residue definition for soil and the metabolites TR-6 and TR-15 are included in the residue definition for water, fully validated analytical methods determining these metabolites in soil and water respectively will be required. (IIA 4.2.2-4.2.3) Evaluation Meeting (15.01.2004): **Data requirement:** **If it is decided that the metabolite TR-4 is included in the residue definition for soil, fully validated analytical methods determining this metabolite in soil will be required.** **Data requirement:** **If it is decided that the metabolites TR-6 and TR-15 are included in the residue definition for water, fully validated analytical methods determining these metabolites in water will be required.**

2. Mammalian toxicology

No.	Column 1 Data point based on draft assessment report or comments from MS	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (i) Co-rapporteur, and (ii) Rapporteur	Column 4 Data requirement or Open Point (if data point not addressed or fulfilled) (Annex point)
(i)	Vol. 3, B.4.1 Proposals for the classification and labelling of the active substance	NL: Based on the results of the 28-day dermal toxicity study in rabbits trifluralin should be labeled with R66.	(ii) The dose tested in the 28-day study was 1000 mg/kg b.w./day, twice the suggested dose by the guideline for testing the skin irritation potential of a substance after a single dermal exposure. In the skin irritation tests where a dose of 500 mg/kg of trifluralin was applied, no irritation was observed after a 4-hour exposure or slight irritation was noted after a 24-hour exposure. Since there are no classification criteria clearly demonstrated in the dir. 67/548/EEC concerning the risk phrase R66 and based on the results of the skin irritation tests, the RMS considers that there is no need for classification of trifluralin for skin irritation. However, this issue could be discussed at the C&L group in Ispra.	-
(ii)	Vol. 3, B.6 Mammalian Toxicology	NL: In general: in majority of the studies, NOELs were derived instead of a NOAEL. Only NOAELs are considered relevant for risk assessment purposes.	(ii) NOELs are derived in studies where greater values are effect level concentrations.	-
(iii)	Vol.3, B.6.1 ADME studies. Bioaccumulation	UK: Only a limited number of tissues were evaluated following multiple oral administration of heptadeutero-labelled trifluralin (on propyl groups). Justification of the limited tissue sampling and the position of the radiolabel must be provided for the repeat dose studies.	(ii) Trifluralin is a lipophilic molecure, with a log Kow at 5.27 (pure 100%) and 4.83 (techn.96.8%) at 20˚ C. Despite the lipophilic nature of the molecure, the evaluation of both single oral and repeated studies showed that there is low bioaccumulation potential in fat. Following multiple oral administration (B.6.1/03) the concentration detected in fat was very low while	-

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	continued		in the liver was below the detection limit of 0,5 ppb. Following single oral administration, trifluralin is almost completely excreted from rat body (88-100%) and minor amounts were detected in the examined organs (<0,6% or <1,75 ppm) or in the carcass (1.54-1.86%). Thus, no evidence of accumulation is expected in other non examined tissues/organs.	
(iii)	Vol.3, B.6.1 ADME studies.			
	Bioaccumulation	The yellow adipose tissue seen at necropsy in the toxicity studies suggests that bioaccumulation occurs.	Concerning the «yellow adipose tissue seen at necropsy in the toxicity studies», this can be explained by the coloured metabolites or trifluralin itself. Bioaccumulation in fat is not expected to occur, since the concentration of radioactivity detected after single oral treatment (0.02-0.03 ppm, 168 hours after administration of single oral dose of 1 mg/kg b.w.) is comparable to that in the repeated administration (0.0097 ppm after administration of 0.5 mg/kg b.w. for 21 days)	
		NL: A rather large amount of the administered radioactivity was excreted in bile. It is not clear whether the in bile excreted radioactivity had been systemically available. One should reconsider the overall oral absorption percentage of 80% and the fact that no correction for systemic availability was used.	The major excretory route for lipohilic compounds, like trifluralin, is bile. The radioactivity in bile is expected to be systemically available, since trifluralin is rapidly absorbed (Cmax in blood was observed at 0,75-1 hours after oral low administration) and slowly eliminated from rat body (β-elimination phase $T_{1/2}$ = 16,3-18,1 hrs). Therefore, trifluralin shows persistence in circulating blood and thus it is likely to take part into the enterohepatic	

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(iii)	*continued* Vol.3, B.6.1 ADME studies. Bioaccumulation		circulation. In other words, the liphophilic metabolites and trifluralin are expected to be systemically absorbed by the intestine or even reabsorbed by the kidneys.	
(iv)	Vol 3, B.6.1/07 Metabolism in the rat and dog.	UK: The evidence that the metabolic pathways in the rat and dog are similar is not conclusive. Although similar metabolites have been identified in the rat and dog, the metabolites have not been adequately quantified in the dog.	(ii) As it mentioned in the DAR (B.6.1/07), «no substantial differences in the metabolic pathway of trifluralin are expected between rats and dogs, based on the similarities of the identified metabolites». No information is provided in the respective study regarding the quantities formed.	-
(v)	Vol. 3, B.6.2.1 Acute oral toxicity	DE: The high vulnerability of newborn rats as compared to adult animals should be adressed and considered in the discussion on a possible need for ARfD setting. Further explanations: PPP containing trifluralin are intended to be applied on crops (cereals, carrots *etc.*) that could be used for baby food preparation.	(ii) Newborn animals are not used for assessing the acute oral toxicity of pesticides according to the existing guidelines. Increased sensitivity of the newborn rats is generally expected. Thus, these data should not be the basis for setting an ARfD according to the respective guidance document.	-

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(vi)	Vol. 3, B.6.2.5 Eye irritation	DE: By the EU (28th time council directive 67/548/EEC), trifluralin has been classified as "Irritant to the eyes" and labelled accordingly (R 36). Further explanations: This apparent contradiction should be clarified by the RMS.	(ii) The classification of trifluralin as irritant to the eye (R36) was decided in the ECB Classification & Labelling – Pesticides Working Group and was introduced in the Annex I of the dir. 67/548/EEC with the 19th ATP. ECB was asked by the RMS concerning the data upon which that decision was based. The relative document (DOC XI/139/85-Add16) was provided by the ECB. Only summary data had been submitted according to which "instillation of a single dose (36 mg) of trifluralin into rabbit eyes caused slight irritation that was cleared within seven days". This statement is in line with the conclusion drawn in the DAR, where several eye irritation studies were presented and evaluated. Among those studies there was one non GLP study (Arthur, 1975) where a single dose of 36 mg of trifluralin was tested and according to which only mild transient eye irritation was observed. This study was considered only as an indicative one since the purity of the test substance tested was not reported. The RMS considers that the classification of trifluralin should be as non irritant to the eyes based on the studies included in the DAR.	-
(vii)	Vol 3, B.6.2.6 Skin sensitisation	UK: We agree the commercial technical material must be classified as a skin sensitiser.		-

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(viii)	Vol. 3, B.6.3.2.1, Oral 90-day toxicity (rat)	DE: The NOEL for subchronic toxicity in the rat should be rather based on a study in male rats with special emphasis on urogenital tract findings that is reported under B.6.8.2 in the monograph. In this study, the NOEL was 2.6 mg/kg bw/d (50 ppm) corresponding well to that one obtained in dogs. NL: It is not clear whether methaemoglobin was included in clinical chemistry investigations. Further explanations: An increase in methaemoglobin was noted in a 1-year study in dogs at 40 mg/kg bw/day.	(ii) RMS agrees with the comment, as it can be shown in the DAR (Summary of short term toxicity) where the overall NOAEL is equal to 2.4 mg/kg b.w./day. This is confirmed by the mechanistic study (B.6.8.2.1/02). In both studies, B.6.3.2.1/01 & B.6.3.2.1/02 methaemoglobin measurements were not included in clinical chemistry examination. The dose of 40 mg/kg b.w./day in the 1-year dog study has been considered as the LOAEL in the DAR.	-
(ix)	Vol. 3, B.6.3.2.2 Oral 90-day toxicity (dog) & Vol. 3, B.6.3.2.3, Oral 1 yr toxicity (dog)	DE: The statement that a 90-day dog study was not conducted is not correct. At least three further subchronic studies in dogs are not mentioned in the monograph. Although they will not substantially change the assessment but rather support the NOEL and the overall conclusions, in particular the one-year feeding study might provide additional information on exposure via the diet. For other fields of toxicological testing, rather old studies are also referred to. Further explanations: The following studies have been submitted by the companies *Hoechst* (later part of *Agrevo* and *Aventis*) and *Montedison* to the German authorities: Bathe, R. et al. : Trifluralin substance technical grade (code: Hoe 38474 O H AT210): 12-month	(ii) The studies referred to by DE were requested by the notifier, who declared that he does not own these studies and he is unable to provide them to the RMS. Consequently, the studies were requested by the German authorities and the RMS awaits for the DE reply.	Open point 2.1: DE authorities to submit the additional subchronic toxicity studies (Annex IIA 5.3.2) Evaluation Meeting (15.01.2004): One MS has asked RMS to contact Task Force since it is for legal reasons not in the postition to submit the required information to the RMS. Task Force has no longer access to the required studies. Therefore, the assessment has to be made on the available data.

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(ix)	*continued:* Vol. 3, B.6.3.2.2 Oral 90-day toxicity (dog) & Vol. 3, B.6.3.2.3, Oral 1 yr toxicity (dog)	oral toxicity (feeding) study in Beagle dogs (Project-Nr. RCC 008864; Study Nr. A29701); 1984, unpublished. Brunk et al.: Toxikologische Prüfung von Trifluralin (Hoe 38474 O H AT204) bei wiederholter oraler Applikation an Beagle-Hunden über 6 Monate (Report Nr. 626/81; Study Nr. A22284); 1981, unpublished. Sterner, W. et al.: 13-Wochen Toxizitätsprüfung von "Trifluralin techn. 95.6%" nach oraler Applikation an Beagle-Hunden (Report-Nr. 2-2-106-76); 1977, unpublished.		Hence, the RMS need to check whether the provision of a 90-day dog study is necessary. Further discussion may take place in an expert meeting. **Open point:** **RMS to check whether the provision of a 90-day dog study is necessary**
(x)	Vol. 3, B.6.3.3.3, percutaneous 28-day toxicity study	NL: Based on the observed moderate-to-severe skin irritation, trifluralin should be labelled with R66.	(ii) The dose tested in the 28-day study was 1000 mg/kg b.w./day, twice the suggested dose by the guideline for testing the skin irritation potential of a substance after a single dermal exposure. In the skin irritation tests where a dose of 500 mg of trifluralin was applied, no irritation was observed after a 4-hour exposure or slight irritation was noted after a 24-hour exposure. Since there are no classification criteria clearly demonstrated in the dir. 67/548/EEC concerning the risk phrase R66 and based on the results of the skin irritation tests, the RMS considers that there is no need for classification of trifluralin for skin irritation. However, this issue could be discussed at the C&L group in Ispra.	-

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(xi)	Vol, 3, B.6.4 Genotoxicity	UK: The requirement for further *in vivo* genotoxicity data is justified. DE: A clastogenic potential of trifluralin is not likely in particular when the in vivo studies are taken into account. In contrast, the possible induction of aneuploidy should be further examined as proposed by the RMS. However, if such an effect would be actually confirmed, the existence of a threshold can be assumed. In this case, special studies like with the benzimidazoles (carbendazim etc.) should be performed to identify the threshold level. Further explanations: A certain likelihood of aneugenic effects is also provided by the fact that cyclization reactions leading to methyl or ethyl derivatives of benzimidazole compounds are part of the rat metabolism. This is a further trigger for requiring a special study. DAS: p.230 An *in vivo* mouse bone marrow micronucleus assay with kinetochore staining is being conducted to a protocol agreed with the RMS. Further explanations: This report is scheduled to be available by the end of October 2003 and will be submitted on request.	(ii) The *in vivo* micronucleus study report has been submitted and evaluated by the RMS (the evaluation of the study is included in the addendum of the DAR, December 2003). Trifluralin did not induce a significant increase in the incidence of micronucleated bone marrow polychromatic erythrocytes or in the incidence of kinetochore positive micronuclei, when administered as a single oral dose to male and female CD-1 mice (5 animals/sex/dose) at doses of 0, 500, 1000, 2000 mg/kg. Hence, trifluralin is considered negative for clastogenic and aneugenic potential in the above test system and under the experimental conditions used. The RMS acknowledges DE for the valid, SAR based, statement on the aneugenic potential of trifluralin.	-

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(xii)	Vol. 3, B.6.5 Long term toxicity and carcinogenicity	DE: The proposal for classification (canc. cat. 3) and labelling (Xn, R 40) is strongly supported. It must be acknowledged that no NOAEL for carcinogenic effects could be established in Fischer 344 rats and that the available information is not sufficient to prove that the tumours are not relevant to humans. Therefore, we agree with the RMS that further mechanistic studies should be required to elucidate the mechanism(s) behind tumour formation. DAS: p277-284 Based on all of the points in our response to the RMS, we maintain that it would be inappropriate to consider trifluralin a possible human carcinogen and assign R40. This opinion is consistent with the decision taken the last time these same data were reviewed at Ispra, when no cancer classification was adopted. Further explanations: For the benefit of other reviewers, the full text of our response to the RMS is provided electronically as "Trifluralin – Carcinogenicity comments to RMS.doc" and accompanies the submission of this comments sheet.	(ii) No classification of trifluralin concerning carcinogenicity was decided by the ECB Classification & Labelling – Pesticides Working Group for the 19 th ATP of the Directive 67/548/EEC. ECB was asked by the RMS concerning the data upon which that decision was based. The relative document (DOC XI/139/85-Add16) was sent by the ECB. Only summary data had been submitted presenting the notifier`s evaluation. RMS`s conclusions in the DAR were based on the evaluation of the full acceptable studies, following the criteria of 67/548/EEC.	-
(xiii)	Vol. 3, B.6.5.1/B.6.5.1.2, Long term oral toxicity and carcinogenicity in the rat *continued:*	UK: The quality of the long-term rat data does not meet modern requirements. A NOAEL has not been determined for the definitive chronic study. Consideration should be given to performing a 2-year chronic/carcinogenicity rat study to modern standards with commercial material of a known technical specification. An upper maximum limit for n-nitrosodipropylamine must be stipulated for	(ii) The RMS has noted that trifluralin chronic toxicity studies are of limited quality. In the 2 year chronic Fischer rat study a NOAEL was not established, since there were findings in rats related to the test substance administration even at the lowest dose level. The performance of a 2 year chronic/carcinogenicity rat study to modern standards with commercial material of a known	Open point 2.2: DE authorities to submit the additional chronic toxicity/carcinogenicity study (Annex IIA 5.5) Evaluation Meeting (15.01.2004):

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(xiii)	*continued:* Vol. 3, B.6.5.1/B.6.5.1.2, Long term oral toxicity and carcinogenicity in the rat	the commercial technical material. DE: Apart from the not acceptable studies described in the DAR, there is a further valid study in Wistar rats that should be also taken into account. However, even though its results (NOAEL 200 ppm, corresponding to ca 10 mg/kg bw/day; no convincing evidence of cancerogenicity) might point to a different sensitivity of rat strains it would remain equivocal which one is the more appropriate model for humans. Further explanations: The following study has been submitted by the company *Hoechst*: Donaubauer et al.: Trifluralin (Code: Hoe 38474 O H AT208): Kombinierte chronische Toxizitäts- und Kanzerogenitätsstudie an Ratten (24 bzw. 28 Monate Fütterungsversuch). Zusammenfassende Darstellung der Ergebnisse und Bewertung. Report-Nr. 86.0092; Projekt-Nr. 680; Studien-Nr. A33023; 1986, unpublished.	technical specification, would provide more reliable information regarding chronic toxicity of trifluralin. The study referred to by DE was requested by the notifier, who declared that he does not own this study and he is thus unable to provide it to the RMS. Consequently, the study was requested by the German authorities and the RMS awaits for the DE reply.	Available study is not sufficient. The NOEL derived from the long term rat study is required. Therefore this study is required. In general the evaluation should be based on the avaiable data only. **Data requirement** **Notifier to submit additional 2-year chronic toxicity/carcino-genicity study in rats** This should be clarified in an expert meeting.
(xiv)	Vol. 3, B.6.5.3, Carcinogenicity study in the mouse	DE: In a further oncogenicity study in mice that is not mentioned in the monograph, a NOAEL of 50 ppm (ca. 7.5 mg/kg bw/day) was established. No evidence of cancerogenicity was obtained. The highest dose level tested was 800 ppm and, thus, well above the top dietary concentration in the only acceptable long-term mouse study used by the Rapporteur. Further explanations:	(ii) The study referred to by DE was requested by the notifier, who declared that he does not own this study and he is thus unable to provide it to the RMS. Consequently, the study was requested by the German authorities and the RMS awaits for the DE reply.	Open point 2.3: DE authorities to submit the additional oncogenicity study (Annex IIA 5.5) Evaluation Meeting (15.01.2004): Risk assessment should be based on available study

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(xiv)	*continued:* Vol. 3, B.6.5.3, Carcinogenicity study in the mouse	The following study has been submitted by the company *Hoechst*: Suter, P. et al.: Oncogenicity study with trifluralin active ingredient technical (Hoe 38474 O H AT210) in mice. Report No.. A32699, Project No. RCC 008853; 1986, unpublished.		available study. No further data necessary.
(xv)	Vol 3, B.6.5.3/01 Mouse carcinogenicity	UK: The dose-related decreases in the incidences of pituitary tumours in female mice and #Leydig cell tumours in male mice indicate that the test material may be an endocrine disruptor. # E Ebert, K H Leist, R Hack and G Ehling. Food Chem. Toxic. Vol 30, No12, pp 1031-1044, 1992.	(ii) Pituitary adenoma was observed in 14/120, 3/80, 3/80 and 0/80 female mice, treated at 0, 563 ppm, 2250 ppm and 4500 ppm dose levels respectively, while testis Leydig cell tumors (benign) were observed in 1/80 mice treated at 563 ppm dose level.	-
(xvi)	Vol 3, B.6.5.1, 6.5.2 & 6.5.3. Tumourigenicity in rats and mice and relevance to human risk assessment	UK: Various tumours have been found in rats (testes, kidney, thyroid and urinary bladder) and mice (liver, lung and stomach). The company have provided plausible mechanisms for the rat tumours but the supporting mechanistic data is equivocal or absent. No mechanisms or mechanistic data have been provided to explain the mouse tumours. Given the weak positive result in the mouse micronucleus study (Gebel *et al*, 1997), these rodent tumours must be regarded as relevant to humans until proven otherwise. CAT: 3 carcinogen (R40) is applicable at the present time	(ii) At macroscopic observation in the mice study (B.6.5.3/01) there was no evidence of carcinogenic effect. The incidences of total benign (pulmonary adenoma in both sexes, skin fibroma in males, pituitary adenoma in females) and malignant (hepatocellular carcinoma in males, and lymphosarcoma in females) neoplasms were reduced, as shown on Table B.6.5.3/01-6 of the DAR. In the 2 year Fischer rat study, clear evidence of trifluralin carcinogenic potential was provided and mechanistic studies, involving the tumor formation observed in the Fischer rat after trifluralin administration, were requested by the RMS in Level 4 of DAR. The weak genotoxic potential in the mouse micronucleus study was not confirmed by a new micronucleus study that was	-

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(xvi)	*continued:* Vol 3, B.6.5.1, 6.5.2 & 6.5.3. Tumourigenicity in rats and mice and relevance to human risk assessment		conducted after the request of the RMS. Thus, carcinogenic effects of trifluralin are not expected to be due to a genotoxic mechanism.	
(xvii)	Vol. 3, B.6.6, Reproductive toxicity	DE: The overall NOEL for reproductive toxicity should be based either on the impairment of reproductive performance or on adverse effects on offspring development but certainly not on parental toxicity. Accordingly, the overall reproductive NOEL for trifluralin should be about 40 mg/kg bw/day rather than 4.5-5.8 mg/kg bw/day.	(ii) The concern of DE authorities on setting an overall NOEL for reproductive toxicity based on systemic parental toxicity, which is not the primary reproductive target, is appreciated. However, it should be noted that pregnant animals may show increased sensitivity and vulnerability to chemicals when compared to non-pregnant animals, due to their different physiological condition. In this case, the NOEL for parental toxicity may be lower than expected for non-pregnant animals. This factor, although not directly associated to an effect of the chemical to the reproductive performance or offspring development, should be certainly taken into account, when setting an overall reproductive toxicity NOEL. This is a policy we generally follow and has been accepted, although there is no specific Guidance Document clarifying this issue.	-

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(xviii)	Vol. 3, B.6.6, Reproductive toxicity (Developmental toxicity/ teratogenicity)	DE: According to the toxicological data package submitted to the German authorities for national registration purposes, the lowest relevant NOAEL for developmental effects was 20 mg/kg bw/day and was obtained in rats. At the next higher dose level of 100 mg/kg bw/day, prenatal losses and developmental retardation were observed. However, this study has been apparently not provided to the RMS. Further explanations: The following study has been submitted by the company *Hoechst*: Baeder et al.: Hoe 38474 - Wirkstoff (Code: Hoe 38474 O H AT210): Prüfung auf embryotoxische Wirkung an Wistar-Ratten bei oraler Verabreichung. Report no. 83.0557, Study no. A27217; 1983, unpublished.	(ii) The study referred to by DE was requested by the notifier, who declared that he does not own this study and he is thus unable to provide it to the RMS. Consequently, the study was requested by the German authorities and the RMS awaits for the DE reply.	Open point 2.4: DE authorities to submit the additional reproductive toxicity study (Annex IIA 5.6) Evaluation Meeting (15.01.2004): RMS to check whether this study is available within one week. Otherwise it will be considered as a data requirement. **Open point** **RMS to check whether the results of the Hoechst study would alter the risk assessment within one week.** **Data requirement** **Notifier to submit study on developmental effects in rats if endpoint of the study is considered essential for further risk calculations.** Open point still open.

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(xix)	Vol. 3, B.6.6.1.1/01 Two generation reproductive study	UK: The incidence of runts has been noted; historical control data are required.	(ii) The incidence of runts was reported in the DAR because there was a suspicion for possible endocrine disrupting effects. However, as presented in the study (Tables B.6.6.1.1/01-3 & B.6.6.1.1/01-5) the incidence of runts, although observed at both generations, did not show a dose-related pattern, was not statistically significant and therefore could not be directly linked to trifluralin administration. At this instance we do not consider that submission of historical control data for the incidence of runts would assist the evaluation process.	See Open point 2.5 Evaluation Meeting (15.01.2004): MS agreed to the RMS's position. **Open point:** **RMS to transfer the summary in column 3 and the attachment to this reporting table into the revised version of the DAR or to an addendum** Open point still open.
(xx)	Vol. 3, B.6.6.1.1/02 Two generation reproductive study	UK: The text refers to 'a few congenital defects were observed in the F1 litters'. These defects need to be listed/tabulated and historical data provided to allow an independent assessment. Uterine atrophy may be related to endocrine disruption.	(ii) The text refers to 'a few congenital defects were observed in the F1 litters, but the dose distribution did not suggest relation to treatment'. These defects were considered as isolated incidences, not dose-related and therefore not essential to be presented in the DAR in detail. However, for your reference a table including F1 litter necropsy data is attached (Table 1). A similar comment was made for F2 litters. Therefore, for clarification purposes a table including F2 litter necropsy data is also attached (Table 2). Uterine atrophy may indeed be related to endocrine disruption. However, this finding alone cannot justify characterisation of trifluralin as an endocrine disruptor.	-

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(xxi)	Vol. 3, B.6.6.1.2/03 Reproduction study in dogs.	UK: Although this study is unacceptable, it is noted that the reported pup deaths at 400 ppm and above include a runt.	(ii) As already mentioned in the DAR, one female runt of the 1000 ppm dose group died overnight. However, this study was of poor quality and it was not possible to fully evaluate this finding. Other pup deaths that occurred during this study were evaluated as accidental.	See Open point 2.5 Evaluation Meeting (15.01.2004): MS agreed to the RMS's position. Open point fulfilled.
(xxii)	Vol. 3, B.6.6.2.1./01 Rat developmental study	UK: The incidence of runts as been noted. Cleft palate is a rare event in rats; historical control data are required. NOAEL for maternal toxicity is 100 mg/kg bw/day based on the dose-related alopecia at 225 and above.	(ii) As already mentioned in the DAR, cleft palate was observed at one fetus from a litter of the 225 mg/kg b.w./day dose group. There were no incidences of cleft palate at 0, 100, 475 and 1000 mg/kg b.w./day. The dose distribution of this finding did not indicate any relation to treatment. Therefore, the RMS does not consider that submission of historical control data for the incidence of cleft palate would further assist the evaluation process. Alopecia is the only effect at 225 mg/kg b.w./day, and although of increasing incidence it is considered as a stress-related finding rather than an adverse effect on health, as it also explained in the DAR. Therefore, it is safe to set a NOAEL of 225 mg/kg b.w./day based on decreased food consumption and body weight gain from 475 mg/kg b.w./day. The NOEL for maternal toxicity is equal to 100 mg/kg b.w./day.	See Open point 2.5 Evaluation Meeting (15.01.2004): MS agreed to the RMS's position. Open point fulfilled.

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(xxiii)	Vol. 3, B.6.6.2.1./02 Rat developmental study	UK: Sparse pathological details for the high number of premature maternal deaths at 750 mg/kg bw/day. No deaths occurred in the previous study at 1000 mg/kg bw/day (Byrd, 1984a). A possible vehicle effect.	(ii) As already mentioned in the DAR, in the study by Borders & Salamon (1985), maternal toxicity at 750 mg/kg b.w./day dose group was evidenced by increased mortality, significant decrease in body weight gain and food consumption, adrenal enlargement and nodule formation and thickening of the forestomach mucosa. Although increased mortality or similar pathology data were not observed in the Byrd (1984a) study when 1000 mg/kg b.w./day trifluralin was administered in pregnant rats, a substantial decrease in net maternal body weight gain (33% less that the control group) indicates that the MTD has perhaps been exceeded. Therefore, although trifluralin administration cannot readily be linked to increased maternal mortality, it appears that trifluralin doses greater than 750 mg/kg b.w./day exceed the MTD for dams, resulting in overt maternal toxicity. Corn oil (the vehicle used in the Borders & Salamon, 1985 study) is a common vehicle used for lipophilic substances in developmental toxicity studies and has never been associated to increased maternal toxicity.	-
~~(xxix)~~ (xxiv)	Vol. 3, B.6.6.2.2./01 Rabbit developmental study	UK: Post-implantation loss/reduced placental weight may be related to endocrine disruption. The incidence of small foetuses has been noted (runts?) Discoloured urine has been dismissed as irrelevant toxicological findings without any explanation.	(ii) Post-implantation loss/reduced placental weight may indeed be related to endocrine disruption. As already mentioned in the DAR, the incidence of small fetuses (< 30 g fetal body weight) was significantly increased among litters of the 120 mg/kg b.w./day group. Trifluralin	See Open point 2.5 Evaluation Meeting (15.01.2004): MS agreed to the RMS's position. Open point fulfilled..

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(xxiv)	*continued:* Vol. 3, B.6.6.2.2./01 Rabbit developmental study		appears to be embryotoxic at a dose of clear maternal toxicity (120 mg/kg b.w./day). The possibility of trifluralin being an endocrine disrupter cannot be excluded. However, there is no sufficient evidence to support this view. Yellow discoloration of the urine appears to be related to excretion of the test substance *via* urine, as already mentioned in the DAR. The intensity of urine discoloration increases with increasing dose, further supporting this view.	
(xxv)	Vol. 3, B.6.6.2.2./02 Rabbit developmental study	UK: The incidence of runts is increased at all dose levels (zero in controls). Abortions at 500 mg/kg bw/day and above. Sex ratio affected at the top dose level.	(ii) As already mentioned in the DAR, the incidence of male fetal runts (< 33.3g) was slightly increased at 100 (3.5%) and 225 mg/kg b.w./day (3.8%) and significantly increased at 800 mg/kg b.w./day (35%). Male fetal runts were not observed at the control and 500 mg/kg b.w./day group. Among female fetuses, there was a slight increase in the incidence of fetal runts at 100 (2.3%) and 500 mg/kg b.w./day (2.9%). As it is obvious from the above data the increased incidence of runts is not dose-dependent. Male sex ratio was slightly decreased at the 800 mg/kg b.w./day dose group. Abortions at doses greater that 500 mg/kg b.w./day were observed. An additional rabbit teratology study was conducted and submitted (see Annex point B.6.6.2.2/03) as a more reliable source of information.	See Open point 2.5 Evaluation Meeting (15.01.2004): Task Force should provide information on endocrine disruptive effect to RMS. RMS should be include information in an addendum. Open point needs to be discussed in an expert meeting. **Data requirement** **Task Force should provide information on endocrine disruptive effect**

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(xxvi)	Vol. 3, B.6.6.2.2./03 Rabbit developmental study	UK: Abortions at 225 mg/kg bw/day and above. High incidence of runts. Sex ratio affected at the top dose level.	(ii) The findings pointed out by UK are confirmed. As mentioned in the DAR, statistical significance was attained only in the incidence of male runts of the 500 mg/kg b.w./day dose group. Possible endocrine disrupting properties of trifluralin cannot be excluded.	See Open point 2.5
(xxvii)	Vol. 3, B.6.3, 6.5 & 6.6 Persistent findings in the toxicity studies.	UK: Both the yellow adipose tissue and the discoloured urine have been dismissed as irrelevant toxicological findings. Please provide an explanation. The incidence of runts/small foetuses in the reproduction studies requires further consideration.	(ii) Trifluralin and its metabolites are yellow colored. As already mentioned in the DAR, yellow discoloration of the urine appears to be related to excretion of the test substance and/or its metabolites *via urine*. The intensity of urine discoloration increases with increasing dose, supporting this view. Moreover, histopathological findings (hyaline droplets, progressive granulonephrosis, calculus, carcinomas) after repeated or prolonged exposure to trifluralin indicate that the target organ is the kidney and justify further excretion of the test substance and / or metabolites in the urine. The yellow adipose tissue is indicative of the lipophilic nature of trifluralin. In the DAR, the incidence of runts was reported in the two generation reproductive study in rats (B.6.6.1.1/01), in the reproduction study in dogs (B.6.6.1.2/03), in the rat developmental toxicity study (B.6.6.2.1/01) and in the rabbit developmental toxicity studies (B.6.6.2.2/01, B.6.6.2.2/02, B.6.6.2.2/03) and is justified in detail under points (xix), (xxi), (xxiii), (xxix), (xxv) and (xxvi) of this Reporting Table.	Open point 2.5: MS to discuss possible endocrine disrupting properties of trifluralin (Annex IIA 5.6) Evaluation Meeting (15.01.2004): MS agreed to the RMS's position. See also point (xxv) Open point fulfilled.

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(xxvii)	*continued:* Vol. 3, B.6.3, 6.5 & 6.6 Persistent findings in the toxicity studies.		Conclusively, although there is limited evidence that the incidence of runts is related to trifluralin administration, after an overall assessment of the test substance, possible endocrine disrupting properties of trifluralin cannot be excluded.	
(xxviii)	Vol. 3, B.6.7 Neurotoxicity	DE: We agree with the Rapporteurs opinion that no neurotoxic properties have to be anticipated for this compound. However, we are aware of a study in chicken further supporting this assumption since it did not provide evidence of delayed neurotoxicity. Further explanations: The following study has been submitted by the company *Hoechst*: Ebert, E. and Leist, K. H.: Trifluralin - Substanz technisch (Code: Hoe 038474 OH ZD 99 0002): Akute Neurotoxizität (acute delayed neurotoxicity) an weissen Leghornhennen. Report no. 85.0742, Study no. A32109; 1985, unpublished.	(ii) The study referred to by DE was requested by the notifier, who declared that he does not own this study and he is thus unable to provide it to the RMS. Consequently, the study was requested by the German authorities and the RMS awaits for the DE reply.	Open point 2.6: DE authorities to submit the additional neurotoxicity study (Annex IIA 5.7) Evaluation Meeting (15.01.2004): The conclusion on the risk assessment can be drawn without additional information on neurotoxicity. No data requirement. Open point fullfilled.
(xxix)	Vol. 3, B.6.8.1 Toxicity studies on metabolites	UK: We agree with the data requirements for the plant metabolites TR-22 and TR-28. DE: In particular with regard to cancerogenic effects of the parent compound, the toxicological relevance of the plant metabolites TR 22 and TR 28 (both not occurring in the mammalian	(ii) According to the Guidance Document on the Assessment of the Relevance of Metabolites in Groundwater (Sanco/221/2000, rev.10, 25-2-03), the toxicity of the plant metabolites of trifluralin, TR-22 and TR-28, should be addressed, since these metabolites are not detected in mammals. At first, an *in vitro* genotoxicity testing battery (it	2.1 Data requirement: *In vitro* genotoxicity and acute oral toxicity tests to be conducted for the plant metabolites TR-22 and TR-28. (Annex AII 5.8.1) Evaluation Meeting (15.01.2004):

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(xxix)	*continued:* Vol. 3, B.6.8.1 Toxicity studies on metabolites	metabolism of trifluralin) must be adressed. To achieve this goal, the proposed genotoxicity tests are considered a first step but are certainly not sufficient. At least, an acute test and a 90-day feeding study should be additionally required to facilitate comparison of the toxicity to the parent. Further explanations: For evaluating a possible cancerogenic potential, QSAR could be also taken into consideration. NL: *In* vitro genotoxicity studies with two plant metabolites TR-22 and TR-28 were requested. However, additional data to establish the toxicological properties of both metabolites should also be requested. Workers might be exposed to these metabolites. DAS: p.333-334 It is concluded that "The relevance of two plant metabolites, TR-22 and TR-28 which were identified in roots of mustard plants at <1% and 1.2% of the total radioactivity respectively and not in metabolism of mammals, should be addressed from a toxicological point of view." and that they "should be checked for their genotoxic potential, by performing at least three *in vitro* tests". We do not believe that this is justified. Further explanations: For the benefit of other reviewers, the full text of our response to the RMS is provided electronically as "Trifluralin – Plant metabolites.doc" and accompanies the submission of this comments sheet.	includes an Ames test, a gene mutation test on mammalian cells and a Chromosome Aberration test) should be conducted on each metabolite. Equivocal results at *in vitro* studies should be substantiated by *in vivo* experiments. Furthermore, in order to address the toxicity of the plant metabolites in comparison with the parent compound, an acute oral toxicity study is required for each metabolite. If the metabolite is of higher oral acute toxicity than the parent compound or it is classified as toxic or very toxic, then the metabolite should be considered as relevant. Moreover, convincing evidence must be provided that these metabolites will not lead to any risk of carcinogenicity (Guidance Document on the assessment of the relevance of the metabolites in Groundwater). The above studies should be always required if the parent compound is classified with Carc. Cat. 3, as it is the case with trifluralin. Pending on the outcome of these studies, the requirement of an additional 90-day feeding study should be decided.	Data requirement essential for unconditional Annex I inclusion. Task Force can provide data on TR-22 by the first quarter of the year 2004. Post meeting EFSA note : alternatively a new metabolism study in oilseeds with identification of the metabolites in the seeds is suggested. **Data requirement:** **Notifier to submit *in vitro* genotoxicity (Ames-test, chromosome aberration test and gene mutation on mamalian cells test ($TK^{+/-}$)) and acute oral toxicity tests for the plant metabolites TR-22 and TR-28 or alternatively metabolism study in oilseeds with identification of the metabolites in the seeds.**

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(xxx)	Vol. 3, B.6.10.2.1, Establishment of ADI	NL: The ADI was based on a 1-year oral study in dogs. A 1-year study in dogs is not considered a chronic study, while the ADI is derived for chronic exposure. This aspect should be addressed.	(ii) The establishment of the ADI based on chronic toxicity studies is a generally followed strategy. However, dog is not tested for life-span toxicity and the NOEL derived from the 1-year dog study is lower than NOELs derived from chronic toxicity studies.	-
(xxxi)	Vol.3, B.6.10.2.2 Establishment of an ARfD	UK: Several effects seen in the developmental studies occur at 120 mg/kg bw/day and above (e.g. deaths, abortions, post-implantation loss). Since these effects may occur after a single dose, an ARfD is essential. Based on the NOAEL of 50 mg/kg bw/day (Rubin, 1986) determined for post-implantation loss and applying a standard safety factor of 100, an ARfD of 0.5 mg/kg bw can be proposed. NL: One might consider the developmental NOAEL of 4.5 mg/kg bw/day for the establishment of the ArfD. Further explanations: The NOAEL of 4.5 mg/kg bw/day was based on decreased offspring growth and survival and decreased ovarian weight at 40.7 mg/kg bw/day. At this latter dose level decreased maternal growth during gestation and lactation, and anemia were noted.	(ii) According to the "Guidance for the setting of an Acute Reference Dose" [document 7199/VI/99 rev.4, 03/01/2001], one of the following categories of toxicological alerts that suggest the need to establish an ArfD, is the following: "Developmental effects, except when these are clearly a consequence of maternal toxicity" As it is clearly stated in the reproductive and developmental toxicity studies in the DAR, there were no teratogenic or fetotoxic effects at non-maternally toxic doses. Deaths, abortions and post-implantation losses have been noted at doses demonstrating clear maternal toxicity. However, apart from the Guidance Document, the necessity of ARfD setting could be re-examined by all Member States. In any case, the ArfD could not possibly be based on a two-generation reproductive toxicity study, as proposed by the NL.	Open point 2.8: MS to discuss the necessity of setting an ARfD (Annex IIA 5.10) Evaluation Meeting (15.01.2004): Open point needs to be discussed in an expert meeting. **Open point:** **Setting of ARfD to be discussed at expert meeting**

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(xxxii)	Vol. 3, B.6.10.2.3 Establishment of an AOEL	UK: Based on the submitted data set, the NOAEL for the 1-year dog study should be used to set the AOEL (but current proposal acceptable). NL: No correction factor for systemic availability was required since oral absorption was established to be > 80%. However, a rather large amount of the administered radioactivity was excreted in bile. It is not clear whether the in bile excreted radioactivity had been systemically available. One should reconsider the overall oral absorption percentage of 80% and the fact that no correction for systemic availability was used.	(ii) According to the Guidance Document for the setting of AOEL levels, no correction factor for systemic availability is required, when oral absorption is set > 80%. Concerning the point for radioactivity in bile, see explanation at point (iii).	-
(xxxiii)	Vol. 3, B.6.10.2.1, B.6.10.2.2, B.6.10.2.3, Reference doses	DE: The proposals for setting the ADI and AOEL are supported. The recommendation not to derive an ARfD is also followed although there are still doubts about acute effects in newborn rats [see comment (v)]. If evidence of aneuploidy induction would be confirmed in the required additional studies, this issue must be reconsidered.	(ii) The required additional genotoxicity study was submitted to the RMS (the evaluation of the study is included in the Addedum of the DAR, December 2003). Evidence of aneuploidy induction was not confirmed.	-
(xxxiv)	Vol. 3, B.6.12/01 Dermal absorption	UK: The dermal absorption data has not been generated with a representative formulation (ethanol vehicle used in the study). The xylene content (approximately 50%) of the commercial formulation could have a marked effect on dermal absorption. Default dermal absorption values must be used for the operator risk assessment until confirmatory data are provided.	(ii) No dermal absorption study was performed with the formulation of trifluralin, which contains xylene. Indeed, xylene is expected to exhibit a marked effect on dermal absorption when applying the undiluted formulation in skin. However, these effects are expected to be mitigated after diluting the formulation with water. Thus, the submitted study (B.6.12/01) performed with a diluted dose of trufluralin in ethanol is considered also as representative for the	-

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(xxxiv)	*continued:* Vol. 3, B.6.12/01 Dermal absorption		diluted commercial product of trifluralin in water. Consequently, for the estimation of Operator exposure levels, the dermal absorption is determined at 10% (default value) for the undiluted formulation and 1% for the diluted and new operator exposure calculations were performed which are included in the Addedum of the DAR (December 2003). The levels of systemic operator exposure were calculated based on the assumptions that retention and absorption of inhaled material is 100% and the dermal absorption degree is 10% for the undiluted product and 1% for the spray dilution. A high application dose/rate scenario (2.5L product/ha – 1.2 kg a.i./ha) and a low application dose/rate scenarios (1L product/ha – 0.48 kg a.i./ha) were considered as in the DAR of trifluralin. For the calculations using UK POEM two cases of spraying volume were considered for each application dose (150 or 600L/ha). Regarding the short term AOEL of 0.026 mg/kg b.w./day, with UK POEM, the estimated values of operator exposure for tractor application scenarios are higher than the AOEL even when protective gloves are worn during mixing/loading and application for all cases. With German Model, the estimated values of operator exposure for tractor application of EF-1521 are lower than the AOEL of 0.026 mg/kg b.w./day when protective gloves are worn during mixing/loading and application for both the low and high dose scenarios	

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(xxxiv)	*continued:* Vol. 3, B.6.12/01 Dermal absorption		and high dose scenarios. In conclusion, there are field application scenarios for formulation EF-1521 for which the operator exposure levels to trifluralin are lower than the AOEL according to the German Model, when the use of protective gloves is considered.	
(xxxv)	Vol. 3, B.6.14.1 Estimation of operator exposure	UK: Although only slightly volatile in its concentrated form, trifluralin is highly volatile on contact with water (H=10.2 Pa m^3 mol^{-1} @20^{O}C) therefore the risk of exposure arising from inhalation of the vapour during spraying should be quantified. DAS: p.392 Table B.6.14.1-7: % of AOEL obtained with UK POEM model should be 'with the German model'	(ii) The volatility of trifluralin in the spraying solution containing the xylene-based formulation cannot be predicted based on the already submitted data. In case, it is considered that there is a risk of exposure for the operator from inhalation of the vapour during spraying, new data must be submitted by the notifier concerning both the volatility of trifluralin in the spraying solution and the estimation of operator exposure.	Open point 2.9: MS to discuss the necessity for the notifier to submit data concerning both the volatility of trifluralin in the spraying solution and the risk of exposure for the operator from inhalation of the vapour during spraying. (Annex IIIA 7.2.1.1) Evaluation Meeting (15.01.2004): RMS's proposal for the data requirement is confirmed. The Task Force should contact the RMS to get detailed information on this issue. **Data requirment:** **Notifier to submit data on volatility of trifluralin in the spraying solution and the risk of exposure for the operator from inhalation of the vapour during spraying**

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(xxxvi)	Vol. 3, B.6.14.3 Estimation of bystander exposure	UK: Bystander exposure has not been quantified. Due to the volatility of trifluralin in water, exposure arising from inhalation of the vapour should be addressed along with dermal and inhalation exposure to the spray.	(ii) The volatility of trifluralin in the spraying solution containing the xylene-based formulation cannot be predicted based on the already submitted data. In case, it is considered that there is a risk of exposure for the bystander from inhalation of the vapour during spraying, new data must be submitted by the notifier concerning both the volatility of trifluralin in the spraying solution and the estimation of bystander exposure.	Open point 2.10: MS to discuss the necessity for the notifier to submit data concerning both the volatility of trifluralin in the spraying solution and the risk of exposure for the bystander from inhalation of the vapour during spraying. (Annex IIIA 7.2.2) Evaluation Meeting (15.01.2004): **Data requirment:** **Notifier to submit data on volatility of trifluralin in the spraying solution and the risk of exposure for the bystander from inhalation of the vapour during spraying** Data requirement essential for unconditional Annex I inclusion.
~~(xxxii)~~ (xxxvii)	Vol. 3, B.6.15 References relied on	DAS: p.406 The report IIA 5.2.1/03 was listed incorrectly in the Summary Dossier as 'N' for Data Protection Claimed. We now wish to claim data protection for this report. p.407 The report IIA 5.2.1/07 was listed incorrectly in the Summary Dossier as 'N' for Data Protection Claimed. We now wish to claim data protection for this report.		-

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(xxxvii	*continued:* Vol. 3, B.6.15 References relied on	p.407 The report IIA 5.2.1/08 was listed incorrectly in the Summary Dossier as 'N' for Data Protection Claimed. We now wish to claim data protection for this report. p.409 The report IIA 5.2.3/02 was listed incorrectly in the Summary Dossier as 'N' for Data Protection Claimed. We now wish to claim data protection for this report.		

3. Residues

No.	Column 1 Data point based on draft assessment report or comments from MS	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (i) Co-rapporteur, and (ii) Rapporteur	Column 4 Data requirement or Open Point (if data point not addressed or fulfilled) (Annex point)
(i)	Vol. 3, B.7.1.1, Metabolism in cotton	UK: Has sufficient characterisation for cotton plants been undertaken, given the residues in various plant parts from N rate application, lipophilic nature of active and high persistent activity in soil?	(ii) This study does not include any characterisation of the radioactive residue. But this is also a comment on the DAR. However, this study gives information on the distribution of Total Radioactive Residue in various plant parts. In addition, besides the lipophylic nature of triflurlin, the a.s. was not found at or above the LOD in seed in all residue trials conducted on this crop.	-
(ii)	Vol. 3, B.7.1.2, Metabolism in Soybean	UK: Has sufficient characterisation for soybean plants been undertaken, given the residues in various plant parts from N rate application, lipophilic nature of active and high persistent activity in soil?	(ii) This study does not include any characterisation of the radioactive residue. But this is also a comment on the DAR. However, this study gives information on the distribution of Total Radioactive Residue in various plant parts. In addition, besides the lipophylic nature of triflurlin, the a.s. was not found at or above the LOD in seed in all residue trials conducted on this crop.	-

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(iii)	Vol. 3, B.7.1.3, Metabolism in mustard	UK: Has sufficient characterisation been undertaken and was methanol a valid primary extraction solvent given that trifluralin solubility was lowest in this solvent?	(ii) In this study characterisation of the radioactive residue was undertaken and gives useful information for the metabolism of trifluralin in various plant parts. Trifluralin was found to be readily soluble in all the organic solvents tested including methanol (142 g/l in methanol). Therefore, to our opinion, the primary extraction using methanol is valid.	-
(iv)	Vol. 3, B.7.1.4, Metabolism in maize	UK: Is this study, together with other studies sufficient to provide such a detailed metabolic pathway in plants? Maize is an 'unusual' cereal and the other studies only looked at TRR (mustard had some characterisation), but the pathway produced is quite complex.	(ii) We do not understand what is meant by the term 'unusual' cereal. According to the working documents, when the metabolism in cereals has to be studied no cereal species are specified as more adequate than others for a metabolism study to be conducted with. This study does provide useful information for distribution and characterisation of the radioactive residue and can be used along with the other studies to provide such a detailed metabolic pathway in plants.	-
(v)	Vol. 3, B.7.2.2 & B.7.2.3, Metabolism in dairy cow and laying hens	UK: Reference made under several studies to Dow AgroSciences unpublished report no. 152. However, these seem to be dated 1965, 1989, 1966 and 1989 (laying hen)	(ii) Indeed, it seems that all these old studies dated from 1965 up to 1989 have been compiled into a report numbered 152. The text should be ammended to include the initial report numbers.	

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(vi)	Vol. 3, B.7.3.1, definition of the residue in plants	UK: Perhaps confirmation of the residue definition should only be made when the toxicological significance of metabolites not found in the rat has been addressed by toxicology data. The metabolism in oily crops was only limited in that no characterisation was made, residues in the oilseed were significant and the relative amounts of the metabolites may be different from those found in the maize crop.	(ii) We do not agree that the confirmation of the residue definition should be based on the toxicological significance of the metabolites not found in rats. To our opinion, these metabolites found in mustard plants (roots i.e. not edible part of the plant) should not be included in the residue definition for the plants covered by this DAR. Toxicological data on these two metabolites may be useful, in the future if other uses are supported. We agree that the metabolism in oily crops was limited due to the fact that no characterisation was made, but this is a comment already stated in the DAR. The residue concentration in seed (oilseed rape) was significantly different from that found in the maize crop only for the second sampling date in oilseed rape. In the first sampling that coincides in the two crops (oilseed rape and maize), the residue level is similar for the same application rate, indicating that the metabolism is similar in the two crops.	Post meeting EFSA note : See section 2, Toxicology, Point (xxix). In case the plant metabolites TR-22 and TR-28 are considered toxicologically relevant a new metabolism study in oilseeds will be necessary. **Data requirement:** **In case the plant metabolites TR-22 and TR-28 are considered toxicologically relevant a new metabolism study in oilseeds will be necessary.**

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(vii)	Vol. 3, B. 7.6	NL: although no residue trials are provided performed in South Europe with oilseed rape, wheat and barley and for sunflower performed in North Europe, after evaluation of additional studies performed in USA/Canada and with over dosage the Netherlands feel that no residues are expected at this GAP for the crops mentioned.	(ii) RMS took notice. This comment is in agreement with the evaluation already submitted.	-
(viii)	Vol. 3, B.7.6.1, residue trials in oilseed rape	UK: In the 1993 OSR trials, the LOQ was very high (0.2 mg/kg), which reduces the value of these trials for risk assessment purposes. Therefore, data from these trials should be discounted, especially as the case made for acceptability of a lack of trials for Southern MS is that residues will not be >0.01 mg/kg.	(ii) The LOQ for **grain**, even in the trials of 1993, is not 0.2 mg/kg but in all cases 0.01* mg/kg. To our opinion, the case made that the residue concentration in grain for S. Europe is not expected to exceed this LOQ is not questionable. The LOQ values for the other plant matrices (straw, plant) are indeed 0.2 mg/kg.	-
(ix)	Vol. 3, B.7.6.2, residue trials in sunflower	UK: Agree with RMS, exceptionally the data from USA can support EU use. This is because of the extremely exaggerated rate which still gave no detectable residues of parent.	(ii) RMS took notice. This comment is in agreement to the evaluation already submitted.	-

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(x)	Vol. 3, B.7.6.4, residue trials in winter cereals (wheat)	UK: Only 4 trials from EU, use of USA/Canada data less robust as GAP not so exaggerated as for sunflower.	(ii) The data package prepared for wheat (4 trials) is sufficient for the support of the use of trifluralin in Northern Europe, since only 2 trials are required in the case of a non residue situation. And here it is clearly a non residue situation. The question is whether the data from US can be used additionally to the 4 European trials to support the extrapolation of residue trials conducted in Northern Europe to South Europe and to our opinion this is possible.	-
(xi)	Vol. 3, B.7.6.4, residue trials in winter cereals (barley)	UK: Only 2 trials from EU. Insufficient data. Use of 3 USA/Canada trials less robust and still insufficient in number for major cereal. Extrapolation of USA data not acceptable. Data from metabolism studies suggest residues much higher than in residue trials but have not been well characterised (except in maize)	(ii) The data package prepared for barley (2 trials) is sufficient for the support of the use of trifluralin in Northern Europe, since only 2 trials are required in the case of a non residue situation. And here it is clearly a non residue situation. The question is whether the data from US can be used additionally to support the extrapolation of residue trials conducted in Northern Europe to South Europe and to our opinion this is possible.	Post meeting EFSA note : **Open point:** **The appropriate number of residue trials for setting MRLs in barley and wheat should be discussed in an expert meeting.**

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(xii)	Vol. 3, B.7.6.4, oats, rye and triticale	UK: Only 4 trials for wheat and 2 trials for barley (all in Northern Member states). The case for extrapolation to oats, rye and triticale needs strengthening as extrapolation is usually acceptable with 8 trials on wheat and barley from Northern and Southern MS. Much of the residues trials package is supported by trials from USA and Canada. However, this is not an accepted standard extrapolation to the EU countries. The overall metabolism package may require further characterisation as this was only carried out in maize.	(ii) The 8 trials is indeed the acceptable number of trials for extrapolation in all cases except when a non residue situation can be justified. In the latter case, the number of trials required can be reduced. Although we agree that this is not acceptable standard extrapolation to the EU countries, such an extrapolation is occasionally done especially for existing herbicides whose residue behaviour is well known. In addition, the data package from US can be used additionally to support the extrapolation of residue trials conducted in Northern Europe to South Europe.	-
(xiii)	Vol. 3, B.7.7, Effects of processing	UK: Although data not evaluated, these data would not allow any effects to be measured as incurred residues were already below the LOQ.	(ii) We agree with the principle that such studies in general hardly can allow any effects to be measured.	-

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(xiv)	Vol. 3, B.7.9, Residues in succeeding crops	UK: It might be useful to include additional information from the studies where characterisation and identification of TRR have been made in the succeeding crops. These data may help to support the primary metabolism studies where characterisation of residues has not been made for oilseed crops. These data may also aid in the case to preclude the requirement for further residues trials data. These succeeding crop metabolism studies are very important to the overall residue data package.	(ii) We agree that it would be useful to include such additional information characterisation and identification of TRR in the succeeding crops if such data was available from the studies submitted. However, as no single component of radioactivity in all studies and all plant parts were found at significant levels, such characterisation was not performed in any of the studies available.	-
(xv)	B7.10 (PHI)	NL: it is proposed that failure of crop growth of oilseed rape and cereals might result in feeding the remaining product, probably containing high levels of trifluralin, to livestock. Therefore, in our opinion an MRL should be set.	(ii) From the residue trials submitted for oilseed rape, indeed there are some trials all conducted in 1993, where the residue level in plants and straw were <0.2 mg/kg. However, we do believe that it is the LOQ of these trials that is high as the rest of the residue trials show residues in plants (potential animal feedingstufs in the case of crop failure) lower than 0.01* mg/kg in all cases. In any case, if considered necessary, RMS will perform the animal intake calculations using as residue concentration for immature plants the value of 0.2 mg/kg, in order to conclude whether an MRLs or a withholding period need to be set	Open Point. If MS considered it necessary, RMS will calculate the animal intake for oilseed rape forage. Evaluation Meeting (15.01.2004): **Open point:** **RMS include calculate the animal intake for oilseed rape forage in an addendum.**

No.	Column 1 Data point based on draft assessment report or comments from MS	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (i) Co-rapporteur, and (ii) Rapporteur	Column 4 Data requirement or Open Point (if data point not addressed or fulfilled) (Annex point)
(xv)	*continued:* B7.10 (PHI)		for products of animal origin for the case of a crop failure. In the EU, cereals are not used as forage crop (cereal forage is also not mentioned in Lundehn, Appendix D, as a forage crop). However, even if a crop failure is considered, from the residue trials submitted for cereals, the residue level in the various plant parts that may be potential feedingstuffs and may be fed to animals in the case of a crop failure (highest residue 0.01 mg/kg in wheat forage at day 52-60) does not result in any case to a significant residue level when animal intake calculations are performed	
(xvi)	Vol. 3, B.7.16.11, Estimation of the Potential and Actual Exposure Through Diet and other Means	DE: The estimation of the acute risk is provisional due to the concerns raised in the toxicological section.	(ii) If an ARfD is considered necessary and is set, then we agree that acute risk assessment will be required and will be performed.	Open Point RMS will calculate the potential acute risk in the case a ARfD is set.(IIA 6.9; IIIA 8.8) Evaluation Meeting (15.01.2004): MS agreed to the RMS's position. **Open point:** **RMS to include a calculation of the potential risk in an addendum in case an ARfD is set.**

No.	Column 1 Data point based on draft assessment report or comments from MS	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (i) Co-rapporteur, and (ii) Rapporteur	Column 4 Data requirement or Open Point (if data point not addressed or fulfilled) (Annex point)
(xvii)	Vol. 3, B.7.12, Proposed MRLs	UK: Assuming residues trials questions are addressed, we would suggest setting the MRLs at an LOQ of 0.05 mg/kg to allow for cost effective monitoring. (It is noted that the UK risk assessments for 0.05 are well within the 0.024 mg/kg bw/day ADI.)	(ii) We agree that setting the MRLs at an LOQ of 0.05 mg/kg will allow a cost effective monitoring, given that the risk assessment is acceptable.	Open Point MS to discuss whether the proposed MRL need to be raised. Evaluation Meeting (15.01.2004): MS agreed to the RMS's position. Open point fulfilled.
(xviii)	Vol. 3, B.7.16.9, Proposed MRLs and Justification for the Acceptability of Those Residues	DAS: Page 497 under the section for treated plants it is stated that "no firm conclusion on residue definition for plants can be drawn." In all other sections in which the residue definition in plants is discussed (e.g., B.7.16.3.1), it is stated that "the residue definition for plants can be restricted to the parent compound trifluralin". Which is correct? We agree with the latter assessment.	(ii) We agree with the latter assessment. The text must be amended.	**RMS to revise the DAR.**
(xix)	Vol. 3, B.7.16.9, Proposed MRLs and Justification for the Acceptability of Those Residues	DAS: Page 497 under the section for food of animal origin, the first sentence was incorrectly copied from a different document since it refers to acetamiprid instead of trifluralin. See section B.7.16.6 – Livestock Feeding Studies for an example of the proper phrasing for the first sentence.	(ii) We agree to this editorial comment. The text must be amended.	**RMS to revise the DAR.**

4. Environmental fate and behaviour

No.	Column 1 Data point based on draft assessment report or comments from MS	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (i) Co-rapporteur, and (ii) Rapporteur	Column 4 Data requirement or Open Point (if data point not addressed or fulfilled) (Annex point)
(i)	Vol.3, B.8.1.1	NL: There is no basis for the estimated values on CO_2 production for the non-covered soil experiment.	We agree with this comment. That's why we use the term *estimated* for the LEVEL of the evolved CO_2 (*ANNEX B, Overall Conclusions, page 520*). The basis for the estimated values on CO_2 production, for the non-covered soil experiment, is not scientific. These estimated values were based on the results of the closed system.	-
(ii)	Vol.3, B.8.1.1	DK : Vol. 3 B.8.1.2.1.b. Page 535. The DT_{50} values at 20°C are estimated to be in the range from 95 – 418 days (mean DT_{50} = 212 days). B.8.1.2.1c. same page : the DT50 values at 10°C are estimated to be in the range from 209 – 920 days (mean DT_{50} = 466 days). According to Danish views such DT_{50} values are unacceptable.	We took notice.	-
(iii)	Vol.3, B.8.1.2.2	NL: The 2nd study described has a history of trifluralin use. Residues of trifluralin were measured in the control field.	We agree with this comment. We have already mentioned in the monograph (ANNEX B, page 544) the presence of residues in the control field. In addition, we had asked for the notifier's justification for the presence of these residues, and finally, we have included his position in the monograph. Nevertheless, the results (e.g. DT_{50} etc) from this study were not taken further into account.	-

No.	Column 1 Data point based on draft assessment report or comments from MS	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (i) Co-rapporteur, and (ii) Rapporteur	Column 4 Data requirement or Open Point (if data point not addressed or fulfilled) (Annex point)
(iv)	Vol. 3, B.8.4.2, photochemical degaradion	Finland: Based on the results presented in Vol 3, point B.8.4.2. the photodegradation of trifluralin in water is shown to be fast resulting to 2 major metabolites TR-6 and TR-15. The toxicity of these metabolites have been tested for fish, daphnia and algae. The toxicity of the metabolites and therefore also the risk from these metabolites was found to be smaller than from trifluralin. However, in Vol 1, in LEVEL 2 and 4 (data requirements) there is a suggestion that the ecotoxicological relevance of these metabolites should be assessed at Member State level. This should be defined more precisely, since if there is some doubt of the risk these metabolites pose, in our opinion this should addressed at EU-level.	It was proposed that the metabolites TR-6 and TR-15 should be further evaluated at Member State level, since the impact of photolysis in the degradation of trifluralin in water is not expected to be the same for all the Member States. The above proposal has not taken into account any eco-toxicological data for TR-6 and TR-15.	**Comment from EFSA:** **As ecotoxicological toxicicity is lower than the toxicity of the parent, the risk assessment of the metabolites is covered by the risk assessment of the parent.** **Open point:** **The ecotoxicological risk assessment of metabolites TR-6 and TR-15 should be confirmed in the expert meeting (ecotoxicology).**
(v)	Vol 1, Point 2.5.2, Degradation in field	Finland: The mean degradation times in field studies in the point 2.5.2. (field dissipation studies) differ from the mean values given in list of end point sheet. Which values are the correct ones?	We accept the comment. The correct mean DT_{50} in LEVEL 2- Point 2.5.2 (Fate and behaviour in soil-Field dissipation studies), is 170 days (and not 164 days). In ANNEX B (page 540) and in the END POINTS List (page 82) the correct mean DT_{50} is given (170 days) instead.	**RMS to revise the DAR**

No.	Column 1 Data point based on draft assessment report or comments from MS	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (i) Co-rapporteur, and (ii) Rapporteur	Column 4 Data requirement or Open Point (if data point not addressed or fulfilled) (Annex point)
(vi)	Vol. 3, B.8.1, Degradation in soil	SE: The mean DT_{50} of 170 days in soil from field studies in DE, UK and USA was used. At least for some of the US studies, the relevance for the EU risk assessment is questionable due to different climatic conditions. Taking only the EU soils into account would give a mean DT50 of 227 days.	We do not agree with this comment. Although the USA field sites were of "*different"* climatic conditions, however they were of "c*omparable to EU region"* climatic conditions. e.g. in the study *Decker, O.D. "Field dissipation of trifluralin following application of Treflan to bare soil and seeded with cotton or soybeans"* the locations were California and Alabama with average temperatures 0- 30° C and 1-32 °C respectively. More climatic details are provided in the respective ANNEXES of the individual studies .	-
(vii)	Vol. 3, B.8.1, Degradation in soil	SE: To be consistent, and to be used for modelling purposes, all DT50 values should be based on 1st order kinetics.	All laboratory and field DT_{50} values were calculated (or re-calculated by the notifier and/or the Rapporteur) using liner or non-linear 1st order kinetics (Tables in ANNEX B page 533, 534, 536, 538, 540).	-

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(viii)	Vol. 3, B.8.1.2.1b, laboratory studies – aerobic degradation at 20ºC	Applicant : By assuming a Q10 factor of 2.2, a DT_{50} of 212 days at 20ºC can be extrapolated from a mean DT_{50} of 181 days at 22ºC. However, the equation given by the RMS on p.535 appears incorrect as it does not give 212 days, but 207 days instead. Please check.	The Q_{10} factor of 2.2 can only be used when we extrapolate to (an unknown) DT50 at θ° C from a (known) DT_{50} at (θ+10)° C. e.g. from $DT_{50(30°C)}$ to $DT_{50(20°C)}$ or from $DT_{50(20°C)}$ to $DT_{50\ (10°C)}$. The equation $\boldsymbol{DT_{50\ (T1)} = DT_{50(T2)} * e^{0.08*\ (T2-T1)]}}$ is correct and is applicable anytime. e.g. if $DT_{50(\mathbf{22}°C)}$ is 100 days then $DT_{50(\mathbf{20}°C)}$ is 117.35, if $DT_{50(\mathbf{23.5}°C)}$ is 100 days then $DT_{50(\mathbf{20}°C)}$ is 132.31, if $DT_{50(\mathbf{30}°C)}$) is 100 days then $DT_{50(\mathbf{20}°C)}$ is 222.55 days (or $DT_{50(\mathbf{20}°C)} \approx Q_{10}$(=2.2) x 100 = 220 days).	-

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(ix)	Vol. 3, B.8.1.2.3, photolysis in soil	Applicant : On p.538, the RMS concluded that the DT_{50} for soil photolysis was 44 days. However, this should be put into context by stating that the comparable DT_{50} for the dark control was 68 days. This then fits in with the conclusion that soil photolysis is not a significant route of degradation, as concluded under B.8.1.1.3 (p. 532).	The Overall conclusions in ANNEX B, page 538, (Rate of photolytic degradation in soil) are: "*Photodegradation of trifluralin on a soil surface under artificial sunlight proceeded with a first-order DT_{50} of 44 days"*. This not controversial with the: "*After 30 days continuous exposure the majority of the applied radioactivity was present as trifluralin. Soil photolysis is not expected to be a significant degradation route for trifluralin in the environment*". (Overall conclusions in ANNEX B, page 532, -Route of photolytic degradation in soil). In addition, the value of 44 days is not considered to be the most accurate for the photolysis rate, since by the end of the experiment (29.8 days) more than 50 % (65.2%) of initially applied trifluralin was found in the irradiated samples as trifluralin unchanged.	-
(x)	Vol. 3, B.8.2.2.3, lysimeter or field leaching studies	Applicant : On p.572, the RMS should mention that an initial attempt has been made using modelling and estimated data to show that the PEC_{GW} for the anaerobic metabolite, TR-4, is <0.1 µg/L.	Accepted.	**RMS to revise the DAR**

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(xi)	Vol. 3, B.8.3, actual and time-weighted average PEC_S	Applicant : On p.573, the RMS uses various field DT_{50} values to calculate the actual and time-weighted average PEC_S values. However, it is more usual to use laboratory data. In addition, a mean field DT_{50} of 170 days is used, when this should be 164 days according to the conclusions under B.8.1.2.2.1 on p.560. Please check.	The background for choosing the mean field DT_{50} value for the estimation of PEC_{SOIL} values was not developed under Point B.8.3- Actual and Time-Weighted Average PEC_S, but could be elaborated to some extend on ANNEX B, page 608, Table B.8.6.3-1, footnote no.1. (*The DT_{50} value (i.e. 181 days) is the mean value of two laboratory studies. In the first study, 3 USA-soil types were used while in the second, 2 Speyer soils were used. However, the second study is old and non-GLP. The RMS would rather prefer the mean DT_{50} value from the field (170 days) to have been used in estimating the PEC_{GW} concentrations; as this value is the mean of 11 soil types (7 European & 4 USA soil types). However, the RMS has accepted the mean $DT_{50\ (lab)}$ value (181 days), as this is greater than the mean $DT_{50\ (field)}$ value (170 days) and so do the estimated PEC_{GW} values).*	**RMS to revise the DAR**

No.	Column 1 Data point based on draft assessment report or comments from MS	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (i) Co-rapporteur, and (ii) Rapporteur	Column 4 Data requirement or Open Point (if data point not addressed or fulfilled) (Annex point)
(xii)	Vol. 3, B.8. Definition of major residues in soil	SE: No major metabolites were observed in aerobic soil degradation studies, but in a soil photolysis and anaerobic soil degradation studies one metabolite occurred at >10% of applied. Generally, we feel that the assessment of major metabolites should be based on aerobic soil degradation studies. However, in cases where photolysis is considered as more important than microbial degradation, these metabolites could be treated equally. For trifluralin exposed to light (spray application to bare soil), photolysis is probably important under environmental conditions, while soil incorporated trifluralin will probably not be exposed to light to a significant extent. Therefor, we propose to include the photolytical product in the definition of the residue only when trifluralin is sprayed onto bare soil. Anaerobic metabolites may be relevant only in certain cases, for example for compounds that leach to deeper soil layers. This is not the case for trifluralin.	*"Irradiation of trifluralin on a soil surface under artificial sunlight did not produce any degradation products ≥ 10% AR. After 30 days continuous exposure the majority of the applied radioactivity was present as trifluralin. Soil photolysis is not expected to be a significant degradation route for trifluralin in the environment".* (*ANNEX B (page 532. Overall Conclusions - Route of photolytic degradation in soil*). So, there were no major photoproducts. In addition, according to the available data, soil photolysis is not considered to be a major route of degradation in soil for trifluralin. Under anaerobic conditions one major metabolite was formed (TR-4). From the proposed GAP, it cannot be excluded that trifluralin cannot be found under anaerobic conditions in soil. These anaerobic conditions are not considered to be relevant only to a few Member States. Therefore, the relevance of the metabolite TR-4 should be addressed at EU level and not at Member State level.	**Open point:** **Data requirements for anaerobic metabolite TR-4 to be confirmed in an expert meeting**

No.	Column 1 Data point based on draft assessment report or comments from MS	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (i) Co-rapporteur, and (ii) Rapporteur	Column 4 Data requirement or Open Point (if data point not addressed or fulfilled) (Annex point)
(xiii)	Vol 3, B.8, page 537	UK: The major soil metabolite TR-4 formed under anaerobic conditions has a data requirement for degradation rate in soil under AEROBIC conditions. We agree with this but consider that the relative importance of anaerobic soil conditions depends on the crop and season of use etc – hence this data requirement should be at MS level.	From the proposed GAP, it cannot be excluded that trifluralin cannot be found under anaerobic conditions in soil. These anaerobic conditions are not considered to be relevant only to a few Member States. Therefore, the relevance of the metabolite TR-4 and the first requirement in LEVEL 4-Point 4.8, page 106 (*A new rate of degradation study for TR-4 is required under aerobic conditions should be provided in case the non-relevance of TR-4 in soil cannot be justified (IIA 7.1.1.2.1)*) should be addressed at EU level and not at Member State level.	See point (xii)
(xiv)	Vol 3, B.8, page 568	UK: For the anaerobic soil metabolite TR-4, soil sorption Koc value has been calculated giving a result of 13600 ml/g. This is very high and suggests that significant groundwater contamination is unlikely. Although, in general, Koc values should be determined experimentally, as TR-4 is formed under anaerobic conditions, we consider this to be sufficient information. Thus the data requirement on page 572 for column leaching on TR-4 is not needed.	We generally agree with the comment. We do not expect that TR-4 could contaminate the ground water, either. However, the K_{OC} value of 13600 for TR-4 is not a *real* (experimental value) but *virtual* value (comes from estimation). We believe that the relevance of the metabolite TR-4 should be addressed at EU level and not at Member State level. And, in the case that TR-4 is found to be biologically active, we believe that the risk assessment for that metabolite should be based on *real* instead of *virtual* values. In addition, we have asked for column leaching data for TR-4 …….only *in case its non-relevance in soil cannot be justified and suitable sorption or other mobility data cannot be obtained*. (LEVEL 2 (page 38) & LEVEL 4 (page 105-106), ANNEX B (568 & 572)).	See point (xii)

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(xv)	Vol. 3, B.8.3, metabolites, initial PEC_S and actual and time-weighted average PEC_S	Applicant : On p. 574, only initial PEC_S values have been provided for the anaerobic metabolite TR-4 because the initial value will provide the greatest soil exposure. This reasoning seems to have been accepted for the aquatic photoproducts TR-6 and TR-15 on p.604 (B.8.6.1), so why not for TR-4 ?	We believe that the metabolite TR-4 should be addressed at EU level. Therefore, full set with PEC_{SOIL} values (Initial, short/long term) are required for the metabolite TR-4, in the case where TR-4 is found to be "a relevant metabolite". We believe that the photoproducts TR-6 and TR-15 should not be addressed at EU level. Therefore, further assessment (e.g. full data for PEC_{SW}, etc) should be done at Member State level.	See point (xii)
(xvi)	Vol. 3, B.8.3, overall conclusions – predicted environmental concentrations in soil	Applicant : The overall conclusions on p.575 should reflect the points mentioned under (4) and (5) above.	The correct mean DT50 value is 170 days. The PEC_{SOIL} calculations were done assuming this value. In LEVEL 2 (page 37), and in ANNEX B (page 560), it was mentioned another value (164 days) instead, which is wrong. However, no further implications are exist due to this mistake. e.g. wrong PECsoil values. We do believe that TR-4 should be evaluate at EU level. The overall conclusions paragraph (page 575) presents fully and correctly our risk assessment.	**RMS to revise the DAR**

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(xvii)	Vol. 3, B.8.4.2, photochemical degradation	Applicant : On p.588, the RMS concludes that the aquatic photoproducts TR-6 and TR-15 should be evaluated at MS level, presumably because the extent of aqueous photolysis varies under different MS conditions. Could this deference to MS assessment also not apply to the anaerobic soil metabolite TR-4, where anaerobic conditions will vary depending upon climate ?	The response hereby is almost the same to a similar UK comment. From the proposed GAP, it cannot excluded that trifluralin cannot be found under anaerobic conditions in soil. These anaerobic conditions are not considered to be relevant only to a few Member States. Therefore, the relevance of the metabolite TR-4 should be addressed at EU level and not at Member State level.	-
(xviii)	Vol. 3, B.8.4.2, quantum yield	Applicant : On p.588, the RMS concludes that the assumptions made in the calculation of the quantum yield are reasonable. Therefore, it would be better to conclude, as under B.2.1.17, that the quantum yield is acceptable (rather than "not accurate") but that it contains an uncertainty, although this does not affect the assessment that trifluralin is photolabile.	We accept this comment.	**RMS to revise the DAR.**

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(xix)	Vol 3, B.8, page 609	UK: The PECgroundwater assessment for metabolite TR-4 uses calculated or assumed worst case values of soil degradation rate and sorption, which indicates that groundwater contamination is unlikely. We accept this but would prefer to see the complete PECgw results provided for all uses and all FOCUS scenarios.	We state (ANNEX B, Page 609): *Two out of the four representative uses submitted for Annex I inclusion were chosen, i.e. spring application to sunflowers and autumn application to winter cereals. For these uses, two FOCUS scenarios were chosen for screening that typically show worst-case leaching, i.e. Piacenza and Hamburg.* No complete data set was submitted with the original study. In the conclusions point of the original study (page 8 of 10) the notifier declared that all PECGW were 0.000 µg/l. It was not considered as necessary to ask for the complete data set, since these values can be checked by at any time by rerunning the FOCUS PELMO.	**Data requirement:** **Notifier to submit for TR-4 a complete set of FOCUS scenarios for the representative uses (oilseed rape, sunflower, cotton).**
(xx)	Vol.3, B.8.4.3.2 Vol.1, LEVEL 2, 2.5.3	NL: An extra water/sediment study with application to the sediment is not considered necessary. UK : The data requirement for another sediment /water study is not needed. There is enough information already available on the major metabolite TR-4 in order to calculate a worst case PECsed (see page 605). This should provide enough information for a basic ecotoxicology risk assessment.	A new water/sediment study to be conducted in two different systems (where the application should be made directly to the sediment) was considered necessary from RMS not only for having sufficient degradation data for the metabolite TR-4 in the sediment, but specially for a further analysis of the non-identified substances which accounted for 27 % at the end of the study (day 100) and which have not been analysed and identified in the existing study.	**Data requirement:** **Notifier to identify non-identified substances in the water/sediment study or to submit a new water/sediment study**

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(xxi)	Vol.3,B.8.4.3.2	SE : The degradation rate in water/sediment systems was calculated by Timme-Frehse/'best fit'-models. Generally, in order to be used for the estimation of time weighted average concentrations, only first order kinetics should be used. In one of the systems, DT50 in the water phase reported to be 13 days, while the whole system DT50 was 3 days. We propose re-calculation to check the reliability of these data. The re-calculation should be based on first order kinetics.	It was not possible to derive a definitive half-life for trifluralin in the water phase because it partitions rapidly to sediment. The DT50 value of 13 days for trifluralin in the water phase is a worst–case calculation from the original water/sediment study. A new water/sediment is required by the RMS, so new DT50 calculations would be available.	Evaluation Meeting (15.01.2004): The active substance is regarded to be persistent with a high potential of accumulation. **Open point:** **DT50 values of the water phase and the whole system in the water/ sediment system need to be discussed in an expert meeting.**
(xxii)	Vol. 3, B.8.5, impact on water treatment procedures	Applicant : On p. 600, the RMS states that no data are provided. However, this point has been adressed as described under Point IIIA, 9.2.2 of the Summary Dossier.	The data provided from the notifier under Point IIIA, 9.2.2 of the Summary Dossier are related to the study on ''Ready biodegradability'' which is included in the monograph under point B.8.4.3.1, Vol. 3.	-

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(xxiii)	Vol.3, B.8.7	DK: Losses of trifluralin due to evaporation accounted for 41, 58 and 67% AR after 24 hours. An evaporation of such a magnitude calls for futher studies to determine the rate of wet/dry deposition down-wind in bordering zones to sprayed areas. The half-life of trifluralin in air is calculated to be 5.3 hours, which is quite sufficient to spread trifluralin to non-target areas at normal wind speed. SE: Trifluralin has a high potential for volatilisation but is reported to be rapidly photolysed in air. However, the metabolites in air should be identified in order to address the risk for long range transport.	The occurence of trifluralin in air is possible because of its high volatility. Therefore, calculation of PEC air was required by the RMS. However, the notifier cannot provide at the present time such calculations since no formal and agreed guidance at EU level is currently available. No metabolites were present in the existing studies on fate and behaviour in air. So, no data on the analysis and identification of metabolites were necessary.	-
(xxiv)	Vol. 3, B.8.8	Applicant : On p.613, the RMS states that a PECair calculation is required. However, since no formal and agreed guidance at EU level is currently available on how to calculate this, and in the absence of a relevant risk assessment end-point, then a PECair value cannot be provided at the present time	The RMS considers the notifier's statement to be reasonable.	-
(xxv)	Vol. 3, B.8.10, definition of the residue	Applicant : On p.623, the RMS should qualify the statement concerning the residue definition in soil so that TR-4 is mentioned only in case it cannot be excluded as relevant from the on-going ecotox studies ?	The metabolite TR-4 was included in the definition of the residue because it was found to be major in soil under anaerobic conditions. The proposed definition of the residue in soil is not considered as final and it is up to the further eco-toxicology evaluation.	-

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(xxvi)	Vol. 3, B.8.10, definition of the residue	Applicant : On p.623, for surface water, since the PEC_{SW} for both the aquatic photoproducts TR-6 and TR-15 are <0.1 µg/L, then these should be excluded even at MS level ?	We believe that the relevance of the aquatic photoproducts TR-6 and TR-15 should be addressed at Member State level.	-
(xxvii)	Vol. 3, B.8.10, definition of the residue	Applicant : On p.623, for sediment, TR-4 should also be qualified to say that it is included only until results of the on-going water/sediment study become available, when it will be reassessed ?	The metabolite TR-4 is considered by the RMS to be a major metabolite in sediment. Therefore, it is included in the residue definition. Its relevancy will be adressed in a later stage.	-

No.	Column 1 Data point based on draft assessment report or comments from MS	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (i) Co-rapporteur, and (ii) Rapporteur	Column 4 Data requirement or Open Point (if data point not addressed or fulfilled) (Annex point)
(xxviii)	General	SE: We noted that this compound is persistent in combination with a high bioaccumulation potential and a high volatilisation. To our opinion, the PB properties alone make the substance unacceptable: -Long persistence and high bioaccumulation potential (in this case also volatilisation) increases the risk for widespread distribution to different environmental compartments, including biota. This implies a higher than normal uncertainty in the estimates of exposure. -Despite the large data package available, unpredictable effects following long-term exposure of biota cannot be excluded when substances are persistent in the environment. This implies a higher than normal uncertainty in the estimates of effects. A high potential for bioaccumulation implies a risk for bioconcentration in various organisms at lower levels of aquatic and terrestrial food chains, and for biomagnification at higher trophic levels. To address the risk for effects from such bioconcentration/ biomagnification would presumably necessitate an impracticable high number of studies.	We took notice.	-

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(xxviii)	*continued:* General	-The expected widespread distribution and the risk for unpredictable effects makes the applicability of point estimates of exposure and effects more uncertain in the risk assessment than for other compounds. -If unforeseen effects eventually would appear, and *ad hoc* risk reduction measures then applied, it could still take a long time to bring down the environmental concentrations to levels at which affected biota can recover. -In this case, the available data package show effects on aquatic organsisms at low levels of exposure, including effects on reproduction, so the problem was not only related to "unpredictable" effects and increased uncertainty.		-
(xxix)	Vol. 3, B.8., general	NL: no comments by RMS are included in the summaries. (Sometimes some comments are stated in the results but the consequences for the quality of the study are never mentioned.)	We preferred to include a suitable comment for the quality and/or the relevance of a study either initially (e.g. for the field studies, where some field studies were not relevant (e.g. GR formulation) and were not taken into account further) or in the results of the individual study (e.g. ANNEX B, page 585, 586). In addition, only were the deficiencies for the whole Annex point considered as significant, we include a suitable comment in the summaries.	-

5. Ecotoxicology

No.	Column 1 Data point based on draft assessment report or comments from MS	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (i) Co-rapporteur, and (ii) Rapporteur	Column 4 Data requirement or Open Point (if data point not addressed or fulfilled) (Annex point)
(i)	Vol. 1, point 2.6.1, Effects on birds and mammals	Finland: Risk assessment for birds are only carried out for birds that eat insects, earthworms and fish. However, application to winter cereals can be performed up to the three-leaf stage. Therefore there is possibility that birds eating young shoots could be exposed and therefore acute and short-term TER-values should be calculated for this exposure scenario also. The acute TER values for mammals should also be calculated. The long-term values for birds and mammals are not relevant, since the application is not during the breeding season.	The critical GAP presented in the DAR is the pre-emergence use on cereals. Although post-emergence applications are currently made to cereals in some countries, this minor use is not being supported in the Annex 1 listing of trifluralin (any mention of post-emergence use in the biology section of the dossier supplied by the Notifier is in error). A risk assessment for post-emergence use is therefore not required.	Evaluation Meeting (15.01.2004): Open point 5.1: RMS to amend the list of end points regarding the GAP. The notifier stated that the post emergence use is not maintained any more. Therefore, the concern of one MS is obsolete. **Open point:** **The risk assemment for birds needs to be discussed in an expert meeting.**
(ii)	Vol. 1, point 2.6.2.1, Effects on fish……	Finland: We do not agree with the chosen chronic NOEC value (25 µg/l), based on the 24 hour exposure, for fish chronic risk assessment. Since the monitoring data show that trifluralin is found quite often from surface water (even in amounts of 0.6 µg/l), it cannot be assumed that the exposure of fish is only to brief exposure for high concentration, followed by rapid dissipation. The exposure can be continuous for low levels of trifluralin and therefore the lowest chronic NOEC value of 0.3 µg/l should be used in risk assessment.	Trifluralin dissipates rapidly from the water phase of sediment:water systems (DT_{50} < 6 hours). It has already been established that vertebral lesions do not result from exposure to the sediments contaminated with trifluralin (Francis & Cocke, 1985) and so the risk assessment depends on a realistic estimate of exposure to trifluralin present in the water phase. Due to its rapid dissipation, the simplest and most representative approach was to compare the endpoint derived from a 24h "peak" exposure plus 1 year development period (i.e. the "24h NOEC" of 25 µg/L) with the maximum initial PEC_{SW} of 2.28 µg/L. This gives a TER_{LT} of 11.	See open point 5.3

No.	Column 1 Data point based on draft assessment report or comments from MS	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (i) Co-rapporteur, and (ii) Rapporteur	Column 4 Data requirement or Open Point (if data point not addressed or fulfilled) (Annex point)
			PEC_{SW} of 2.28 µg/L. This gives a TER_{LT} of 11. Alternatively, the risk assessment could be conducted by comparing the TWA concentration of trifluralin with the 35-day NOEC of 0.3 µg/L, in line with recommendations in the Guidance Document SANCO/3268/2001. The 35-day TWA, based on an initial concentration of 2.28 µg/L and a DT_{50} of 6 hours, is 0.023, µg/L which leads to a TER_{LT} of 13. The TER_{LT} values for chronic risk, whether based on a brief exposure to a peak concentration followed by a long development period or a chronic exposure to low concentration, both exceed the Annex VI trigger of 10. Consequently, there is no unacceptable risk.	

No.	Column 1 Data point based on draft assessment report or comments from MS	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (i) Co-rapporteur, and (ii) Rapporteur	Column 4 Data requirement or Open Point (if data point not addressed or fulfilled) (Annex point)	
(ii)	*continued:* Vol. 1, point 2.6.2.1, Effects on fish……	Further explanations The assumption that fish are only acutely exposed to trifluralin is not correct. The monitoring data show constant low levels of trifluralin in surface waters (other compartments not studied). Trifluralin is also present at sediment and suspended solids and as the study B.9.2.3/02 show, trifluralin is accumulated to fish even though it is bound to sediment (BCF 1087-1838). Most probably trifluralin will also be accumulated to fish by biomagnification through food web. Therefore the assumption that chronic risk assessment could be based on a one day acute exposure data as in draft assessment report has been done is not acceptable.	With regard to the monitoring data cited, it is not appropriate to compare a single maximum value from a monitoring data set with a chronic endpoint obtained under continuous exposure conditions. 0.6 µg/L was the maximum value obtained from a data-set of 1,959 samples. Compared to the "peak" NOEC of 25 µg/L, this does not indicate a cause for concern ("TER" 42). If the highest median concentration of 0.0025 µg/L is compared to the chronic exposure NOEC of 0.3 µg/L, this also does not indicate a cause for concern ("TER" 120). Study B.9.2.3/02 has been cited to support the argument that chronic exposure conditions (as indicated by accumulation in tissues) must be taken into account when assessing the development of vertebral lesions in fish. The key finding of this study, however, was that, despite some bioaccumulation occurring, this did not cause any vertebral lesions in the treated fish. Consequently, the risk assessment does not need to be modified on this account.		

No.	Column 1 Data point based on draft assessment report or comments from MS	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (i) Co-rapporteur, and (ii) Rapporteur	Column 4 Data requirement or Open Point (if data point not addressed or fulfilled) (Annex point)
(ii)	*continued* Vol. 1, point 2.6.2.1, Effects on fish……	We also do not agree with the explanation that the result of crooked ribs and vertebral lesions observed in the study with fathead minnows could be overlooked since same effects were not seen at the same concentrations in rainbow trout early-life toxicity test or sheephead minnow full life toxicity test. In our opinion the results only show that there is difference in the sensitivity of different fish species. The NOECs obtained with rainbow trout and sheephead minnow were at the same level than with fathead minnow, but the most sensitive end points were different.	The point of the objection is not clear. It was not the intention to propose that the vertebral lesions and crooked ribs observed in the fathead minnow should be overlooked on the grounds that similar effects were not seen in studies on rainbow trout and sheepshead minnow at similar exposure levels. In fact, in one of the studies on sheepshead minnow (Crouch et al, 1979), vertebral dysplasia was observed. The chronic NOEC for all species is generally around 1 µg/L, even though this may not always be based on the incidence of vertebral lesions/crooked ribs. In the study providing the lowest endpoint (0.3 µg/L, Meyerhoff et al. 1992), the effects seen at 3.2 µg/L and below were classed as minimal to slight (i.e. no external distortion of the body). The variation in NOEC is therefore more likely due to variation in the subjectivity of assessment rather than species sensitivity. In conclusion, the intent was not to disregard the effects seen in the fathead minnow study, but to assess the relevance of the exposure conditions causing such effects. The critical endpoint of 0.3 µg/L is valid in the context of a quality standard (if long-term exposures were to occur) but is not valid in this risk assessment where the fate and behaviour characteristics of trifluralin are such that exposure levels in the water phase will not remain at initial levels for long periods.	

No.	Column 1 Data point based on draft assessment report or comments from MS	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (i) Co-rapporteur, and (ii) Rapporteur	Column 4 Data requirement or Open Point (if data point not addressed or fulfilled) (Annex point)
(iii)	Vol. 3,B.9.2.1.acute toxicity to fish.	DK: The acute study-part of some of the chronic studies with the standard species of fish, done under static conditions, are not mentioned in the monograph under acute toxicity (B.9.2.1). In these studies it is evident, that the lasing chronic damage, (spinal cord deformities,) besides mortality, takes place within 24 hours exposure or perhaps within four hours. So we suggest, that the acute $LC_{5024hours}$, besides mortality, also include spinal deformities, which in nature means certain death. Therefore the $LC_{5024\ hours}$ for spinal deformities for *Salmo trutta* should be calculated. Further explanation DK: Volume 3. Page 696. In a study (from 1985) 15.4, % 59.3 % and 100 % of groups of around 75 brown trout (*Salmo trutta*) died after transfer to uncontaminated water for five months after a stay for 24 hours exposed to initial nominal concentrations of 25, 100 and 250 microgr. trifluralin/l, respectively. All fish exposed to 100 and 250 microgr. trifluralin/l "were prostrate or showed signs of swimming impairment after five hours of exposure. After 24 hours some fish exposed to these concentrations had dark dorso-ventral markings, which were suggested to be due to haemorrhage from spinal lesions" Percent trifluralin related column deformities were 3.2 %, 95,8 % and 100 %, respectively (see also below under chronic toxicity).	There is no such endpoint as an "LC_{50} for spinal deformity" (LC_{50} is the median lethal concentration). It is agreed, however, that short-term exposure to trifluralin could lead to lasting chronic damage. That is why a risk assessment based on the "24h NOEC" (24 h exposure followed by a 1 year period to observe spinal deformities) was conducted. The conclusion of this risk assessment was that the risk was acceptable (TER>10). See previous comments	See open point 5.3

No.	Column 1 Data point based on draft assessment report or comments from MS	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (i) Co-rapporteur, and (ii) Rapporteur	Column 4 Data requirement or Open Point (if data point not addressed or fulfilled) (Annex point)
(iii)	*continued* Vol. 3,B.9.2.1.acute toxicity to fish.	**NOEC in this study for vertebral damage was 25 microgr./l, nominal.** **Half-life in the water was 6.5 – 8.7 hours in the test aquariums**. The acute $LC_{5024\ hours}$ is less than 100 microgr. Trifluralin/l for *Salmo trutta* in this study. This $LC_{5024\ hours}$ from a static test with *Salmo trutta* of less than 100 microgr./l compares well with the $LC_{5024\ hours}$ of 95,4 microgr. Trifluralin/l.from a 96 hour acute toxicity flow-though study with rainbow trout, *Oncorhynchus mykiss*. (Volume 3, B.9.2.1. page 667.) This demonstrates, that the effects from exposure to trifluralin take place within the half life of trifluralin in the water column	This is the endpoint that was used in the chronic risk assessment	-

No.	Column 1 Data point based on draft assessment report or comments from MS	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (i) Co-rapporteur, and (ii) Rapporteur	Column 4 Data requirement or Open Point (if data point not addressed or fulfilled) (Annex point)
(iv)	Vol. 3,B.9.2.2. Chronic toxicity to fish.	DK: The chronic end point of % spinal damage should be regarded as an acute end point in the risk assessment (see above) and compared to the initial PEC. Further explanation DK: On page 695 of volume 3 it is mentioned, that in *Pimephales promelas* **a concentration-dependant increase in spinal column compression was significant at a mean measured conc. of 0.7 microg. triflualin/l…** suggesting chronic damage under flow-though conditions in 35 days. The chronic NOEC was calculated to 0.3 microgr. trifluralin/l. It should also be mentioned here, that the max. value of trifluralin found in UK rivers in 1989 in the analysis of potentially dangerous substances was 0.226 microgr/l. **Max values of trifluralin in surface waters reported from Belgium, France, Greece and the UK are in the range of 0.2 – 0.7 microgr./l.**	There is no such endpoint as an "LC_{50} for spinal deformity" (LC_{50} is the median lethal concentration). It is agreed, however, that short-term exposure to trifluralin could lead to lasting chronic damage. That is why a risk assessment based on the "24h NOEC" (24 h exposure followed by a 1 year period to observe spinal deformities) was conducted. The conclusion of this risk assessment was that the risk was acceptable (TER>10). See previous comments See previous comments See previous comments	See open point 5.3

No.	Column 1 Data point based on draft assessment report or comments from MS	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (i) Co-rapporteur, and (ii) Rapporteur	Column 4 Data requirement or Open Point (if data point not addressed or fulfilled) (Annex point)
(v)	Vol. 3 Annex B-9.1.7 Summary and risk assessment (birds)	UK: In the first tier risk assessment for fish-eating birds, it is considered that a worst case residue estimate in fish should be used, derived by multiplying the fish bioconcentration factor by the surface water predicted environmental concentration (PECsw) from spray drift at 1 metre. Currently the PECsw value used in this calculation relates to that from spray drift contamination when risk mitigation in the form of a 5 metre no-spray buffer zone is included. Further explanation It is not considered appropriate to derive an estimate of active substance residue levels in fish in the first tier risk assessment by multiplying the 5 metre no-spray zone surface water initial PEC (i.e. 2.28 µg a.s./l) by the bioconcentration factor (5674). Instead the 1 metre PECsw value of 11.08 µg a.s./l should be used, this resulting in worst case fish residue levels of 63 mg a.s/kg fish, with TERs for fish-eating birds of approximately a fifth of those estimated in Tables B.9.1.7.08 to B.9.1.7.10. It is acknowledged however that these revised TERs will still be within Annex VI triggers.	The risk assessment will be re-calculated assuming spray-drift across 1 m. In accordance with the latest version of SANCO/4145/2000, the 3-week TWA PECsw (instead of the initial PECsw), as the risk assessment for fish-eating birds has a meaning only for chronic exposure, should be used to determine residue levels in fish for the tier 1 assessment. This will result to even higher TER values. The initial PECsw was used as the worst "non realistic" proposal. Since a 5m "no-spray zone" is indicated as mitigation against risks to aquatic organisms, this scenario will still be retained as an option for higher tier risk assessment.	Open Point 5.2 Evaluation Meeting (15.01.2004): **Open point:** **RMS to revise the risk assessment for fish eating birds in an addendum.** Open point still open.

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(vi)	Vol. 3 Annex B-9.2.5/01 Field monitoring pond mesocosm study	UK: It is considered that this study is not reported in sufficient detail in Vol. 3 to support the conclusions drawn. No justification is included as to how a field study conducted in central Indiana is representative of European conditions. Further explanation The results of the trifluralin field monitoring pond mesocosm study are briefly reported, with e.g. no details supplied for the range of species of fish collected at the treated site or for their individual numbers. The level of detail supplied is insufficient to support all of the conclusions drawn at the end of this section and is not adequate to support the statement included in the endpoint table that the 'tier 2' chronic risk assessment 'is substantiated by the findings of an extensive field monitoring study'. It is also doubtful whether the results of one field monitoring study conducted in central Indiana would be sufficiently representative in terms of climate and soil type to European conditions.	The study is presented as supporting information, lower tier risk assessments having already demonstrated "no unacceptable risk". The additional details referred to are available and all Member States have direct access to the full report. However, for convenience, the summary report if needed could be expanded in the DAR. There is no reason to doubt the relevance of this pond study any more than the relevance of any other pond study. The catchments area was an agricultural site based on silt loam and silty clay loam soils. Row cropping covered 60% of the area with average slopes of 2.5-6% and steep slopes of 10-20%. Indiana is on the same latitude as central Spain/southern Italy.	-

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(vii)	Vol.3, Annex B.9.2.8 Summary and risk assessment.	UK: The results of the aquatic chronic toxicity studies (summarised in Table B.9.2.8-03) suggest that the fathead minnow (*Pimephales promelas*) may be more sensitive to the effects of trifluralin than rainbow trout (*Oncorrhynchus mykiss)*. Therefore it is considered that the reported short-term exposure sub-lethal effect study with juvenile brown trout should have ideally been repeated using the fathead minnow. We consider that a strengthened argument for the chronic risk assessment is required.	Due to its rapid dissipation, the simplest and most representative approach was to compare the endpoint derived from a 24h "peak" exposure plus 1 year development period (i.e. the "24h NOEC" of 25 µg/L) with the maximum initial PEC_{SW} of 2.28 µg/L. This gives a TER_{LT} of 11. Alternatively, the risk assessment could be conducted by comparing the TWA concentration of trifluralin with the 35-day NOEC of 0.3 µg/L, in line with recommendations in the Guidance Document SANCO/3268/2001. The 35-day TWA, based on an initial concentration of 2.28 µg/L and a DT_{50} of 6 hours, is 0.023, µg/L which leads to a TER_{LT} of 13. The similarity of this TER to the one derived from the "peak" exposure scenario is reassuring. A repeat test (with a vertebrate species) is not considered to be necessary. The TER_{LT} values for chronic risk, whether based on a brief exposure to a peak concentration followed by a long development period or a chronic exposure to low concentration, both exceed the Annex VI trigger of 10. Consequently, there is no unacceptable risk.	Open Point 5.3 Evaluation Meeting (15.01.2004): One MS disagreed with the RMS. **Open point:** **RMS to include the revised risk assessment on fish, mentioned in the reporting table, in an addendum to be discussed in an expert meeting.** Open point still open.

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(vii)	*continued:* Vol.3, Annex B.9.2.8 Summary and risk assessment.	Further explanation The chronic risk assessment for fish is ultimately based on a short-term exposure study on juvenile brown trout (NOEC 25 µg/l based on an assessment of spinal column abnormalities). The initial chronic risk assessment was based on a more recent flow-through juvenile growth test on fathead minnow, which gave a NOEC of 0.3 µg a.s./l based on spinal abnormalities. The approximate 85-fold decrease in sensitivity might well have been influenced by the reduced exposure period in the trout study, but it is unfortunate that this study was not repeated using fathead minnow or that time-to-effect information is not available from the fathead minnow study. It is possible in this instance that brown trout are not such a sensitive species and that the usual 10-fold uncertainty factor is not sufficient.	The TER_{LT} derived from a comparison of the TWA exposure and the chronic endpoint of 0.3 µg/L (from the most sensitive species) also exceeds the Annex VI criterion of 10.	-
(viii)	Vol. 3, B.9.1.7, Risk assessment for birds	SE: We noted that the short term and the long term risk assessments for birds were based on the dietary concentrations. This should be corrected to daily dose, in accordance with the guidance document.	Although the practice of converting dietary concentration to daily dose was not commonly accepted, the DAR will be amended accordingly.	Open Point 5.4 Evaluation Meeting (15.01.2004): **Open point:** **RMS to include endpoints based on daily doses for birds in DAR and list of endpoint.** Open point still open.

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(ix)	Vol. 3, B.9.2.8, Risk assessment for aquatic organisms.	SE: We do not agree with the selected NOEC for the refined risk assessment for fish; The long term NOEC of 25 µg/L was obtained from a study where juvenile brown trout were exposed for only 24 hours (acute exposure), and then observed for up to one year. From our point of view, these data cannot over-rule the results from studies with chronic exposure. Besides, the most sensitive species from those tested in standard chronic studies was not brown trout but fathead minnow (NOEC 0.3 µg/L).	Due to its rapid dissipation, the simplest and most representative approach was to compare the endpoint derived from a 24h "peak" exposure plus 1 year development period (i.e. the "24h NOEC" of 25 µg/L) with the maximum initial PEC_{SW} of 2.28 µg/L. This gives a TER_{LT} of 11. Alternatively, the risk assessment could be conducted by comparing the TWA concentration of trifluralin with the 35-day NOEC of 0.3 µg/L, in line with recommendations in the Guidance Document SANCO/3268/2001. The 35-day TWA, based on an initial concentration of 2.28 µg/L and a DT_{50} of 6 hours, is 0.023, µg/L which leads to a TER_{LT} of 13. The TER_{LT} values for chronic risk, whether based on a brief exposure to a peak concentration followed by a long development period or a chronic exposure to low concentration, both exceed the Annex VI trigger of 10. Consequently, there is no unacceptable risk.	Open Point 5.5 Evaluation Meeting (15.01.2004): See open point 5.3

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(ix)	*continued:* Vol. 3, B.9.2.8, Risk assessment for aquatic organisms.		In conclusion, the intent was not to disregard the effects seen in the fathead minnow study, but to assess the relevance of the exposure conditions causing such effects. The critical endpoint of 0.3 µg/L is valid in the context of a quality standard (if long-term exposures were to occur) but is not valid in this risk assessment where the fate and behaviour characteristics of trifluralin are such that exposure levels in the water phase will not remain at initial levels for long periods. The TER_{LT} values for chronic risk, whether based on a brief exposure to a peak concentration followed by a long development period or a chronic exposure to low concentration, both exceed the Annex VI trigger of 10. Consequently, there is no unacceptable risk.	
(x)	Vol. 3, B.9.3.2, Risk assessment for mammals	SE: The study referred to for the selection of NOAEC for mammals seems to be wrong. In the study reported under B.6.5.1/01, did not include a test concentration of 200 ppm. The selection of reproduction endpoint should be clearly justified.	The NOAEC of 200 mg/kg was actually derived from the 13-week study only. In view of the incidence of renal tumours occurring in the lowest treatment group (813 mg/kg diet) in the 2-year study (I07), it was considered prudent to adopt 200 mg/kg diet for both exposure periods. In the event (i) the 13-week study is the more relevant exposure period for a wildlife risk assessment for chronic exposure of trifluralin and (ii) there is now no longer a need to obtain separate endpoints for "short-term" and "long-term" exposure for mammals. The critical endpoint remains 200 mg/kg diet (equivalent to 10.7 mg/kg bw/day).	-

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(xi)		SE: We noted that the short term and the long term toxicological endpoints for mammals were based on dietary concentrations. This should be recalculated to daily dose, in accordance with the guidance document.	The justification for selecting this endpoint is: A special 13-week study in Fischer rats (IIA 5.8.2, Ref. D01) was undertaken to establish an NOEC for effects on the kidney and hence an NOEC for the neoplastic changes seen after lifetime exposure in this strain of rat (IIA 5.5.1, Ref. I07). Detailed investigations of kidney morphology and function comprised urinalysis, including protein electrophoresis, and renal histopathological examinations. The NOAEC for kidney changes was 200 ppm, equivalent to a dosage of 10.7 mg/kg bw/day, based on minimal to slight cortical tubular intracytoplasmic hyaline droplet formation. Urinalysis was normal at this concentration. This is considered an appropriate NOAEC for short-term to long-term exposure to wild mammals. The chronic LOAEC was 813 mg/kg, equivalent to a dosage of 30 mg/kg bw/day, based on renal transitional cell carcinoma in two male rats (3.4%) at this dosage. These renal tumours arose by a non-genotoxic mode of action and did not occur in female Fischer rats, two other strains of rat or mice. Although the practice of converting dietary concentration to daily dose was not commonly accepted, the DAR will be amended accordingly.	Open Point 5.6 Evaluation Meeting (15.01.2004): **Open point:** **RMS to include endpoints based on daily doses for mammals in DAR and list of endpoint.**

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(xii)	Vol. 3, B.9.9.3, Risk assessment for non-target plants	SE: Due to the high persistence of trifluralin in soil, the possible risk for effects on the succeeding crop should be addressed.	The possible risk for effects on the succeeding crop is recognised and dealt with under B.3.2.8 Minimum waiting periods or other precautions between last application and sowing or planting succeeding crops - Limitations on choice of succeeding crops (Annex IIIA 3.8).	-
(xiii)	Vol. 3, B.9.11, References relied on	SE: The list of references for this section seems to be incomplete.	Agreed. Not all of the studies, which have been summarised in the DAR, have been included in the reference list. DAR to be amended accordingly.	Open Point 5.7 Evaluation Meeting (15.01.2004): **RMS to complete the reference list in the DAR.** This point is considered to be fulfilled.

No.	Column 1 Data point based on draft assessment report or comments from MS	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (i) Co-rapporteur, and (ii) Rapporteur	Column 4 Data requirement or Open Point (if data point not addressed or fulfilled) (Annex point)
(xiv)	Vol. 3, B.9.1 Effects on birds	NL: - acute risk: For the acute risk assessment a small insectivorous bird (amongst others) has been chosen. But to estimate the ETE the RUD value for large insects has been taken. In the opinion of NL the RUD value for small insects (52) is the right value for the risk assessment for birds. This is also according to the Guidance Document on Risk Assessment for Birds and Mammals. However, it will not change the conclusion that there is a low risk for insectivorous birds. - short-term risk: Also here the RUD value for small insects (29) must be taken for the risk assessment for insectivorous birds. According to the Guidance Document the toxicity value and the exposure value have to be expressed in mg a.s./kg bw. - long-term risk: Also here the RUD value for small insects (29) must be taken for the risk assessment for insectivorous birds. According to the Guidance Document the toxicity value and the exposure value have to be expressed in mg a.s./kg bw.	Agreed, if foliar applications were to be made. However, applications of trifluralin are made pre-emergence to bare soil. Larger, ground-dwelling insects are therefore the likely food item for birds. Regardless of this argument, the relevance of RUD values, based on foliar applications, to residues taken up from treated soil is questionable. The relevant RUD for soil-dwelling insects for acute toxicity is 1 (90%), for short and long term toxicity is 0,1 (50%) (Aldenberg and Jaworska (2000) according to the Guidance Document on Risk Assessment for Birds and Mammals, Appendix II-9, Table 10. According to the same Guideline there is no exposure for insectivorous mammals for the proposed crops according to the GAP (i.e. “early application” to cereals). An alternative approach would be to adopt the same procedure for soil-dwelling insects as used for earthworms i.e. calculate residues using the BCF equation of Jager. Although this equation was derived for earthworms, it is likely to be highly conservative for insects, given the less permeable nature of insect cuticle. The DAR will be amended accordingly.	Open Point 5.8 Evaluation Meeting (15.01.2004): **See open point 5.1**. This point is considered to be fulfilled.

No.	Column 1 Data point based on draft assessment report or comments from MS	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (i) Co-rapporteur, and (ii) Rapporteur	Column 4 Data requirement or Open Point (if data point not addressed or fulfilled) (Annex point)
(xv)	Vol. 3, B.9.2 Effects on aquatic species	NL: Chronic risk assessment: There are two reproduction studies with two species of *Daphnia*. The 21-day NOECs from these two studies showed a large difference (NOEC-values of ≥ 50.7 µg as/L and 0.1 µg as/L). Is there an explanation for this difference?	This non-GLP study (*Daphnia similis*) clearly does not fulfil the quality criteria required of a GLP study. There was no verification of test concentrations (a guideline requirement) and there were numerous and major reporting inconsistencies. Consequently, the validity of the results is questionable. The study was presented for the sake of completeness only.	-

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	continued: Vol. 3, B.9.2 Effects on aquatic species	The chronic toxicity endpoint for fish has been changed from 0.3 to 25 µg/L in the refined chronic risk assessment. This is, according to the RMS, substantiated by the findings of an extensive field monitoring study. In this field study only run-off events occurred. Because trifluralin adsorbs fast to sediment there will not be much exposure of fish by the water phase. But when contamination of surface waters occurs through spray drift there will be exposure of fish by the water phase and effects can occur. NL agrees with the RMS that the exposure time will be short but sublethal effects can already be induced within a short period. Therefore NL has doubts if the endpoint should be changed from 0.3 to 25. To solve this point it is recommended to ask the notifier for a chronic water/sediment study with fish (static test) to mimic realistic conditions.	The field monitoring study is presented essentially to provide supplementary and supporting information and is not crucial to the risk assessment. The original chronic risk assessments was conducted on the basis of a brief exposure followed by a long-term recovery to identify potential chronic effects, as this is the most appropriate scenario for exposure in the environment. This is in agreement with the comment "*NL agrees with the RMS that the exposure time will be short but sublethal effects can already be induced within a short period.*" The endpoint relevant to this type of exposure is 25 µg/L and therefore it is not clear how this comment can be used to support the case that there are "*doubts if the endpoint should be changed from 0.3 to 25 µg/L*". There is no need to repeat the study although, an alternative chronic risk assessment has been conducted to confirm the low risk. The TER from a comparison of the TWA exposure and the chronic endpoint of 0,3 µg/L also exceeds the Annex VI trigger of 10.	See open point 5.3

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	continued: Vol. 3, B.9.2 Effects on aquatic species		The influence of sediment in the test system has already been assessed. In a study conducted with sediment-bound trifluralin, no evidence of vertebral dysplasia was found in fish exposed to trifluralin concentrations up to 12,500 µg/kg, even after frequent stirring of the sediment to de-sorb the trifluralin (Francis & Cocke, 1985, B.9.2.3/02). This finding is essentially supported by the results from the field monitoring study.	-
(xvi)	Vol. 3, B.9.2 Effects on aquatic species	NL: Bioaccumulation It is stated that there is rapid elimination of trifluralin from fish tissues. This is not confirmed by the field monitoring study in which the half life of trifluralin in several fish species was determined to range from 15 – 30 days. However, from the risk assessment on birds and mammals it appeared that there is low risk to fish-eating birds and mammals using high BCF-values, so it can be concluded that the criteria for bioaccumulation are met.	No comment required	-
(xvii)	Vol. 3, B.9.3 Effects on other terrestrial vertebrates	NL: For assessing the short-term and long term risk the toxicity value and the exposure value have to be expressed in mg a.s./kg bw, according to the Guidance Document.	Although the practice of converting dietary concentration to daily dose was not commonly accepted, the DAR will be amended accordingly.	Open Point 5.9 Evaluation Meeting (15.01.2004): See open point 5.6.

No.	Column 1 Data point based on draft assessment report or comments from MS	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (i) Co-rapporteur, and (ii) Rapporteur	Column 4 Data requirement or Open Point (if data point not addressed or fulfilled) (Annex point)
(xviii)	Vol. 3, B.9.5 Effects on other arthropod species	NL: It is mentioned that the trigger for all the studies is 50%, according to ESCORT 2. But the 50% trigger is only valid for extended laboratory and (semi-)field tests. For first tier laboratory tests a trigger value of 30% is used. If there are LR50-values for *Aphidius rophalosiphi* and *Typhlodromus pyri* available a HQ-value can be calculated, but for trifluralin this is not the case. Using the trigger of 30% there is also a risk for *Phygadeuon trichops* (34.1%). However, this will not change the conclusions and NL can agree with the conclusion that there is a low risk for non-target arthropods, in-field as well as off-field.	It is widely accepted since the adoption of ESCORT 2 that the trigger value for glass plate tests is 50% effect on mortality. This is in part a consequence of the use of a Hazard Quotient (HQ) in the tier I risk assessment. The HQ is calculated from the ratio of the maximum field application rate and the LR50 for either indicator species (*Aphidius rhopalosiphi* or *Typhlodromus pyri*). If the ratio (HQ) is below 2 then the product is classified as low risk to non-target arthropods. In common with other areas of ecotoxicology, a limit test may be conducted at the maximum field rate. In such cases, the LR50 (or similar) may be expressed as greater than the highest rate tested. This value is then used in the HQ (or TER) calculation. In the case of non-target arthropods, 50% or less effect at the maximum use rate will lead to an HQ of 1 or less, indicating no risk. In addition, since the 50% trigger is used for extended laboratory and higher tier tests, it is not logical, consistent or protective to keep the ESCORT 1 trigger of 30% for glass plate tests. Consequently the 50% trigger should be applied to all studies. In the specific case of *Phygadeuon trichops* it should be noted that the test was performed using a non-standard species and guideline and did not include a toxic reference treatment. Furthermore, the method has not been ring-tested. At best, this test can only be used as supplementary information and does not indicate a high level of risk of trifluralin to arthropods. It should not be used for risk assessment.	-

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(xix)	Vol. 3, B.9.6 Effects on earthworms	NL: Because the log Kow of trifluralin > 2, a correction factor of 2 for the organic matter content (from 10% to 5%) must be applied. The LD50 values will be divided by a factor of 2 and the TER-values will be two times lower. The conclusions of the acute risk assessment will not change, but regarding the chronic risk for earthworms it is not sure that the trigger of 5 will be exceeded (the TERlt $\geq$ 3), so a refined risk assessment or a new chronic study with a sufficient high concentration is necessary.	Agreed. According to Guidance Document SANCO/10329/2002, a refinement of exposure should be considered before turning to higher tier tests. In the sub-acute study, the test material was applied at the rate of 7,245 g as/ha (15 L/ha) to vessels of 200 cm^2 surface area containing 500 g soil (dry weight). This equates to an actual soil concentration of 28.98 mg as/kg dry soil in the study, which in turn leads to a TER_{LT} of 9 after applying the additional factor of 2. According to the recommendation for refinement given in the Guidance Document, the risk is therefore considered to be acceptable. The DAR will be amended accordingly.	Open Point 5.10 Evaluation Meeting (15.01.2004): **Open point:** **RMS to revise the risk assessment for earthworms in an addendum.**
(xx)	Vol. 3, B.9.7.1 Organic matter breakdown	NL: it is concluded that in the litter bag test there was no evidence of any adverse effects on organic matter degradation arising from treatment with EF-1521, when applied at the maximum field rate of 2.5 L/ha (1200 g ai/ha). But also the toxic reference (methyl bromide) gave no adverse effects on the organic matter breakdown. Therefore the results of this study are questionable.	The unreliable nature of positive controls in this type of study was discussed extensively at the EPFES (Lisbon) workshop organised to review and agree on the optimal design for a litter bag study. The recommendation of the workshop was that a positive control was too unreliable and no longer required. Consequently, the results of the study on EF-1521 cannot be considered questionable on the basis of the performance of the positive control. If the study were to be repeated, a positive control would not be included, according to current requirements.	-

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(xxi)	Vol. 1, level 2	NL: The comments mentioned above regarding Volume 3, Annex B, are also relevant for volume 1, level 2.	Agreed. The DAR will be amended accordingly.	Open Point 5.11 Evaluation Meeting (15.01.2004): **RMS to revise DAR and list of endpoints for the above mentioned points.**
(xxii)	Endpoint list	NL: Effects on earthworms Toxicity values which are corrected for the organic matter content, must be mentioned in the list. The results of the litter bag test must be mentioned in the endpoint list.	Agreed. The DAR will be amended accordingly.	Open Point 5.12 Evaluation Meeting (15.01.2004): **RMS to revise the list of endpoints.**
(xxiii)	Vol. 1, level 4: 4.9 Ecotoxicology	NL: - a refined risk assessment regarding the chronic risk to earthworms or a new sublethal toxicity study with earthworms with a sufficient high concentration is necessary.	According to Guidance Document SANCO/10329/2002, a refinement of exposure should be considered before turning to higher tier tests. In the sub-acute study, the test material was applied at the rate of 7,245 g as/ha (15 L/ha) to vessels of 200 cm^2 surface area containing 500 g soil (dry weight). This equates to an actual soil concentration of 28.98 mg as/kg dry soil in the study, which in turn leads to a TER_{LT} of 9 after applying the additional factor of 2. According to the recommendation for refinement given in the Guidance Document, the risk is therefore considered to be acceptable. The DAR will be amended accordingly.	Open Point 5.13 Evaluation Meeting (15.01.2004): See open point 5.10.

Attachment to the Reporting table, trifluralin (Hb) *EU RESTRICTED*

16134/EPCO/BVL/03, rev. 1-1 (15.01.04)

section 2

Reporting Table Section 2, point No. (xix)

B.6.6.1.1/02 Two generation reproductive study

Summary of F1 and F2 litter necropsy data, in response to the respective UK comment.

Table 1. F1 litters necropsy data

Triflurex dietary concentration (ppm)	**Control**	**50**	**450**	**4000**
Necropsy data (No. of fetuses affected/No. of litters affected)				
No. of fetuses / litters examined	310/24	309/24	319/25	267/25
Right kidney hydronephrosis	8/7	2/2	2/2	0/0
Intestine distended with gas	3/3	0/0	7/5	2/2
Hemorrhagic peritoneum	2/2	1/1	2/1	1/1
Hemorrhagic urinary bladder	0/0	0/0	1/1	0/0
Hemorrhagic intestine	0/0	0/0	2/2	1/1
Diaphragmatic hernia	0/0	0/0	1/1	0/0
Right lung solid dark color	0/0	0/0	1/1	0/0
Left eye enlarged; lens malformed	0/0	0/0	0/0	1/1
Small right eye	0/0	0/0	0/0	1/1

Table 2. F1 litters necropsy data

Triflurex dietary concentration (ppm)	**Control**	**50**	**450**	**4000**
Necropsy data (No. of fetuses affected/No. of litters affected)				
No. of fetuses / litters examined	329/24	309/24	337/24	254/24
Right and/or left kidney hydronephrosis	7/5	8/6	0/0	0/0
Agnathia	1/1		0/0	0/0
Right and/or left kidney distended	2/2	1/1	0/0	0/0
Intestine distended with gas	1/1	0/0	0/0	2/1
Hemorrhagic kidney	0/0	1/1	0/0	0/0
Hemorrhagic urinary bladder	0/0	0/0	2/1	0/0
Hemorrhagic intestine	0/0	0/0	3/1	0/0
Brachygnathia	0/0	0/0	0/0	1/1