PEER REVIEW REPORT ON **SPIRODICLOFEN** 09 06 2009

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REPORT OF EPCO EXPERT MEETING 26

SPIRODICLOFEN

Rapporteur Member State: The Netherlands

Specific comments on the active substance in the section

4. Environmental Fate and Behaviour

are already listed in the relevant reporting table. Comments submitted for this meeting are listed below.

1. Comments submitted for this meeting:

Date	**Supplier**	**File Name**
None		

2. Documents submitted for meeting:

Date	**Supplier**	**File Name**
December 2004	RMS/The Netherlands	Spirodiclofen consultation report
04 March 2005	RMS/The Netherlands	Spirodiclofen reporting table rev1-1
May 2005	RMS/The Netherlands	Spirodiclofen list of essential studies B8 B9
May 2005	RMS/The Netherlands	Spirodiclofen list of end points B8 B9
May 2005	RMS/The Netherlands	Spirodiclofen addendum vol1 vol3 B8 B9
23 May 2005	RMS/The Netherlands	Spirodiclofen evaluation table rev0-1

3. Documents tabled at the meeting:

Date	**Supplier**	**File Name**
None	Name	

The conclusions of the meeting were as follows:

4. **Data on preparations:** Complete.

5. **Classification and labelling:** Candidate for R53.

6. **Recommended restrictions/conditions for use:** None concerning Fate and Behaviour alone; confirmation of acceptable risk is a decision made by Ecotoxicology (EPCO 27)..

7. **Reference List** The meeting did not identify a need to amend the list of studies and information relied on dated May 2005.

Areas of concern: None

Appendix 1: EPCO discussion table: SPIRODICLOFEN

Appendix 2: Evaluation table

Appendix 1: Discussion Table, Spirodiclofen (In)

4. Environmental Fate and Behaviour

No.	Subject	Discussion EPCO Expert Meeting	Conclusions EPCO Expert Meeting
	Open point 4.1: MS to discuss in an expert meeting which interception values should be used for PEC soil calculation. (see reporting table 4(1))	A comment was received querying whether the FOCUSsw values should be used for crop interception. However, experts agreed that it was worse-case and therefore acceptable to use the 50% value. The generic issue of use of FOCUSgw interception values for production of PECsoil was discussed. Different approaches are adopted by different MSs, with some using the maximum of 50% specified by the Directive in the absence of experimental data, whereas others routinely use the higher interception values supported by FOCUSgw. Following discussions, experts agreed that it is appropriate to use the FOCUSgw interception values because they are supported by crop-specific data and have been endorsed by MSs for use in gw calculations. However, it is also appropriate to use more simple worst-case assumptions (e.g. 0% interception) where this conservative estimate results in an acceptable risk assessment.	Open point fulfilled.
	Open point 4.2: RMS to clearly indicate acceptability and reliability of the studies in an addendum or corrigendum. (see reporting table 4(3), 4(4), 4(5) and 4(6))	Open point actioned by RMS. However, the conclusions on the acceptability of the studies in column C of the evaluation table need to be transferred to the addendum. As a general point, NL requested that RMSs ensure that it is clearly stated which studies are considered acceptable and for what purpose. Experts agreed.	Open point still open: RMS to transfer the conclusions on the acceptability of the studies in column C of the evaluation table to the addendum.
	Open point 4.3: RMS to clarify in B.8.9 and in the list of end points (p 107) the residue definition in	The endpoints have been updated and this was noted in the addendum.	Open point fulfilled.

No.	Subject	Discussion EPCO Expert Meeting	Conclusions EPCO Expert Meeting
	ground water (separated of surface water). (see reporting table 4(9))		
	New open point 4.4	Following discussions on column C of Point 4.1. Experts raised the issue of the approaches used for DT50 selection for the metabolites in the PECsoil calculations, which appeared to be inconsistent. NL to check that the calculations had been performed with the correct assumptions (the endpoints and addendum summary tables of DT50 values contain errors which need to be corrected by the RMS – see conclusion column).	RMS to update endpoints and addendum tables of soil DT50 values to include the correct values for metabolite BAJ 2740-dihydroxy (29.5 days) and BAJ2740-ketohydroxy (27 days). RMS to verify that the PECs were calculated using the appropriate values.

Appendix 2: Evaluation table

4. Environmental Fate and Behaviour

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the evaluation group
	Section 4 Data requirements: **-** Open points: ***3***			Section 4 Data requirements: **-** Open points: ***2***
	Open point 4.1: MS to discuss in an expert meeting which interception values should be used for PEC soil calculation. (see reporting table 4(1))	The RMS re-calculated PEC soil with an interception rate of 50 %. According to the EU guidance document 95/36/EC, this default worst case value should be used "unless actual experimental data give more specific information". The FOCUS working group provides such specific information, i.e. interception rates of 65 % for apple, 70 % for citrus and 40 % for grape. These crop-specific interception values should be used to calculate PEC soil values. In the PECsoil calculations, a DT50 of 29.5 d (rather than 49 d) should be used for BAJ 2740-dihydroxy, and a DT50 of 10 d (rather than 21 d) should be used for BAJ 2740-ketohydroxy in Fresno soil; please see BCS **position paper 4_1** (Kaune, A., 2005a; BCS Document no MO-05-006081).	May 2005: We don't consider the interception values from the FOCUS groundwater group to be 'specific information on actual experimental data'. Therefore we think the PECs values calculated according to the EU guidance document 95/36/EC using the default value for the fraction reaching the soil correct. Further inspection of the study and the raw data shows that a DT_{50} of 49d. is indeed too worst case. It can be agreed to use the value of 29.5 d. In a position paper BCS questions the use of the upper limit of c.i. as DT_{50} value after recalculation by RMS using Modelmaker instead of ACSL. This can	Open point fulfilled.

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the evaluation group
	continued Open point 4.1: MS to discuss in an expert meeting which interception values should be used for PEC soil calculation. (see reporting table 4(1))		be agreed upon. Considering the recommendations by FOCUS kinetics (which of course has not been accepted) the mean value of the modelmaker calculations should be used, DT_{50}=14d.	
	Open point 4.2: RMS to clearly indicate acceptability and reliability of the studies in an addendum or corrigendum. (see reporting table 4(3), 4(4), 4(5) and 4(6))	In the notifier's opinion, the studies mentioned in 4(4), 4(5) and 4(6) of the reporting tables are reliable and acceptable. Concerning reporting table 4(4), the study is reliable and acceptable with respect to establishing the route of degradation. The same metabolites as with the dihydrofuranon label (investigated by Oi and Bornatsch, 1999) were found. No additional metabolites exceeded 10 % AR. The pathway established with the dihydrofuranon label was confirmed in this study, using a different label position. Concerning reporting table 4(5), the Notifier agrees with the RMS that the	May 2005: 4(4) The report by Oi (1999a) provides acceptable information on the route of degradation with another label position. In the study no DT_{50} values were provided and these were not recalculated by RMS. The values from the study by Oi and Bornatsch (1999) were considered more reliable. 4(5)The aged leaching column study is a reliable study and provides useful information on metabolites in the column leachate. However, if the data are used to derive Koc values there are some shortcomings that make the Koc values less reliable for further use in a risk assessment.	Open point remains open: RMS to transfer the conclusions on the acceptability of the studies in column C of the evaluation table to the addendum.

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the evaluation group
	continued Open point 4.2: RMS to clearly indicate acceptability and reliability of the studies in an addendum or corrigendum. (see reporting table 4(3), 4(4), 4(5) and 4(6))	study is acceptable. Concerning reporting table 4(6), the comments from the RMS in the DAR clearly show that the experimental conditions of the photolysis study (Hellpointer, E. 1998a) do not have a negative impact on the results. Hence, the study is reliable and acceptable.	4(6) The study by Hellpointer (1998a) was designed to determine the quantum yield of photolysis in water and should be considered acceptable for that. The DT_{50} that is derived from this study should be considered less reliable and as better data are available these data should not be used for risk assessment. This will be made clear in a corrigendum.	
	Open point 4.3: RMS to clarify in B.8.9 and in the list of end points (p 107) the residue definition in ground water (separated of surface water). (see reporting table 4(9))	The residue definition for water is spirodiclofen (BAJ 2740) and BAJ 2740-enol. A separate residue definition for ground water should include only the parent compound because the 80th percentile concentration in groundwater according to FOCUS-PEARL is ≤ 0.001 µg/L for BAJ 2740-enol for all scenarios.	May 2005: The residue definition for surface water is the parent and BAJ 2740-enol. For groundwater it is only the parent. The endpointslist has been amended as such. In B8.9 this should be clarified in a corrigendum.	Open point fulfilled.
	New Open point 4.4 This open point was identified at the EPCO 26 meeting.			RMS to update endpoints and addendum tables of soil DT50 values to include the correct values for metabolite BAJ 2740-dihydroxy (29.5 days) and BAJ2740-ketohydroxy (27 days). RMS to verify that the PECs were calculated using the appropriate values.

REPORT OF EPCO EXPERT MEETING 27

SPIRODICLOFEN

Rapporteur Member State: The Netherlands

Specific comments on the active substance in the section

5. Ecotoxicology

are already listed in the relevant reporting table. Comments submitted for this meeting are listed below.

1. Comments submitted for this meeting:

Date	**Supplier**	**File Name**
21 February 2005	Germany	Spirodiclofen com01 DE

2. Documents submitted for meeting:

Date	**Supplier**	**File Name**
December 2004	RMS/The Netherlands	Spirodiclofen consultation report
04 March 2005		Spirodiclofen reporting table rev1-1
May 2005		Spirodiclofen list of essential studies B8 B9
May 2005		Spirodiclofen list of end points B8 B9
May 2005		Spirodiclofen addendum vol1 vol3 B8 B9
23 May 2005		Spirodiclofen evaluation table rev0-1

3. Documents tabled at the meeting:

Date	**Supplier**	**File Name**
xx Month xxxx	Name	

The conclusions of the meeting were as follows:

4. **Data on preparations:** BAJ 2740 240 SC

5. **Classification and labelling:** R52/R53

6. **Recommended restrictions/conditions for use:** MS to consider appropriate risk management for bees and aquatic life using appropriate Annex V phrases

7. **Reference List**

Areas of concern: Bees, Aquatic life

Appendix 1: EPCO discussion table: SPIRODICLOFEN

Appendix 2: Evaluation table

Appendix 1: Discussion Table, Spirodiclofen (In)

5. Ecotoxicology

No.	Subject	Discussion EPCO Expert Meeting	Conclusions EPCO Expert Meeting
			Section 5 Data requirements: ***3*** Open points: ***9***
	Confirmation of GAP	Orchards and Vines 1 app/season. Orchards 144 g a.s./ha vines 96 g a.s./ha. Single formulation 'BAJ 2740 240 SC'	
	Open point 5.1: RMS to prepare an addendum to clarify if further data is needed to address the risk to aquatic organisms or not. (see reporting table 5(3))	New data submitted. (fish + Daphnia chronic studies). Full risk assessment presented in new addendum. Acute risk has not changed and is acceptable (p 18 addendum). Long term risk – Table 2.6.2.7 TERs low, fish BZ 50 m, lower BZ for other crop (first tier). Notifier proposed use of TWA s:10 day Daphnia, 65 day fish – RMS proposed not to use TWA approach, this was agreed. NOEC for fish based on growth effects in ELS flow through study. Refinement further study on rainbow trout pulsed dose in water/sed study NOEC of 20 µg/l. New study with Daphnia 11.1 µg/l. New RA using these studies BZ still need for some uses. NOT proposes to use 21 day TWA for *Daphnia*. RMS proposes to accept TWA , smaller BZ still required. Meeting agreed to use fish NOEC of 20 µg/ and compare with a peak PEC, since the behaviour of the a.s. in the study matched that seen in the water/sed study. According to the guidelines no chronic study is required but for such a compound it was agreed that chronic studies were necessary. Meeting agreed to use new flow through Daphnia study with an initial PEC since time to effect cannot be determined in such a study.	Open point 5.1 fulfilled. New open point 5.10. RMS to establish how the sensitive life stage of fish was determined for the ELS test. New Open point 5.11: RMS to amend list of endpoints (TERs to be recalculated comparing NOECs for fish and *Daphnia* with initial PECs)
	Open point 5.2: RMS to amend the list of endpoints regarding the BCF (add or adjust based on total radio-activity). (see reporting table 5(6))	BCF endpoint amended.	Open point 5.2 fulfilled.

No.	Subject	Discussion EPCO Expert Meeting	Conclusions EPCO Expert Meeting
	Open point 5.3: RMS to prepare an addendum with a revised risk assessment for birds and mammals according to the final version of the Guidance Document on Birds and Mammals to be discussed in an expert meeting. (see reporting table 5(7))	Provided in new addendum. Birds: oversprayed insects, drinking water and earthworms and fish-eating birds. For fish eating bird assessment meeting agreed that values used in Table 2.6.1.1-1 were worst case. Drinking water assessment should have been conducted using 20% dilution and not the surface water PEC, but in this case the TERs are so high that it will not make a significant difference. Metabolite enol RMS considers studies with parent cover the risk. Bioaccumulation of enol logPow 3 therefore assessment provided table 2.6.1.1-2, TER >5, therefore risk to birds from enol metabolite is low. This was agreed. 3 major soil metabolites (2.4-dichloroenzoic acid, BAJ 2740-ketohydroy and BAJ 2740-dihydroxy), no evidence that studies with parent would cover these. Assessment for each provided in addendum. This was accepted. Mammals: (Table 2.6.1.2-1) Long term risk for mammals feeding on short grass. (TER<5). Refinement: Repro NOEC 6.0 mg a.s./kg bw/d slight effects at LOEC 350 mg a.s./kg diet (2 gen study). RMS therefore proposes to use relevant endpoint based on the LOEC which is equivalent to 29.6 mg a.s./kg bw/d. On page 11 of DAR the LOEC is stated to equivalent to 26.2 mg a.s./kg bw/d. Meeting agreed on the value of 26.2 mg a.s./kg bw/d. RMS to amend assessment to include correct value. Enol Metabolite. Risk acceptable. Soil metabolites. NOEC values taken to be equivalent to parent. Risk to earthworm eating mammals acceptable.	Open point 5.3 fulfilled. New Open point 5.12: RMS to amend list of endpoint with respect to the Mammalian repro LOEC of 350 mg a.s./kg diet (26.2 mg a.s./kg bw)
	Open point 5.4: RMS to prepare an addendum with a revised risk assessment regarding bioaccumulation using the BCF-value based on total radioactivity (BCF of 491 L/kg). (see reporting table 5(9))	Done. Included in new risk assessment. See open point 5.3.	Open point 5.4 fulfilled.

No.	Subject	Discussion EPCO Expert Meeting	Conclusions EPCO Expert Meeting
	Open point 5.5: MS to discuss the setting of the NOEC for mammals in an expert meeting. (see reporting table 5(12))	Done. See open point 5.3	Open point 5.5 fulfilled.
	Open point 5.6: RMS to transfer information (avian toxicity) from column 3 of the reporting table to an addendum to be discussed in an expert meeting. (see reporting table 5(19))	Done. Presented in addendum. In mammals endocrine effects appears to be non specific. Meeting agreed with arguments proposed by RMS in new addendum	Open point 5.6 fulfilled.
5.1	Notifier to address the effects on bee brood (e.g. a field study, labelling). (see reporting table 5(24))	No new data. The meeting agreed to the risk mitigation measures proposed by the RMS. The product should be labelled as follows: No use during flowering of the crop and avoiding that flowering crops are present (e.g. mowing the weeds).	Data requirement fulfilled (provided labelling is practical)

No.	Subject	Discussion EPCO Expert Meeting	Conclusions EPCO Expert Meeting
	Open point 5.7: RMS to transfer information regarding risk to other non-target arthropods from column 3 of the reporting table to an addendum to be discussed in an expert meeting. (see reporting table 5(25))	Done. See p 29 Addendum. *T pyri* and *C carnea* less sensitive than target insects. suggests that specificity to target organisms is high. Meeting agreed that appropriate routes of exposure were covered for this IGR compound.	Open point 5.7 fulfilled.
	Open point 5.8: MS to discuss the risk to NTA in an expert meeting. (see reporting table 5(26))	Done. See Open point 5.7.	Open point 5.8 fulfilled.
5.2	Notifier to submit the new chronic study with fish. (see reporting table 5(35))	Done.	Data requirement fulfilled.
	Open point 5.9: MS to discuss the chronic risk to aquatic organisms in an expert meeting. (see reporting table 5(35))	Done See 5.1	Open point 5.9 fulfilled.

No.	Subject	Discussion EPCO Expert Meeting	Conclusions EPCO Expert Meeting
5.3	Notifier to submit summary on endocrine effect on fish to the RMS. (see reporting table 5(41))	Presented in addendum. ELS study using enol metabolite was originally presented for German National registration where an EC10 of 21 µg enol metabolite/l was determined. Sex ratio affected by death of male fish. Germany to supply Netherlands with their evaluation. There is no opportunity to return the discussion to an EPCO meeting.	Data requirement fulfilled. New Open point 5.13: RMS to consider German national assessment of the ELS study using the enol metabolite.
	Residues Definition	Soil: parent spirodiclofen +2.4-dichlorobenzoic acid Water: parent spirodiclofen + enol (dependent upon outcome of fish ELS study)	

Appendix 2: Evaluation table

5. Ecotoxicology

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the evaluation group
	Section 5 Data requirements: ***3*** Open points: ***9***			Section 5 Data requirements: **-** Open points: ***4***
	Open point 5.1: RMS to prepare an addendum to clarify if further data is needed to address the risk to aquatic organisms or not. This new open point was proposed at the EPCO 27 meeting (see reporting table 5(3))	The use pattern of spirodiclofen with a single seasonal application as well as the very fast dissipation from surface water (<2 d) indicates that chronic exposure of aquatic organisms is unlikely. However, the toxicity observed under chronic exposure conditions has been taken into consideration and a full risk assessment has been provided by the notifier, including risk mitigation options.	May 2005: The toxicity observed under chronic exposure conditions has been taken into consideration and a full risk assessment has been provided in the addendum of May 2005. Open point fulfilled.	Open point 5.1 fulfilled. New open point 5.10. RMS to establish how the sensitive life stage of fish was determined for the ELS test. New Open point 5.11: RMS to amend list of endpoints (TERs to be recalculated comparing NOECs for fish and *Daphnia* with initial PECs)
	Open point 5.2: RMS to amend the list of endpoints regarding the BCF (add or adjust based on total radio-activity). (see reporting table 5(6))		May 2005: The list of endpoints has been amended regarding the BCF. Open point fulfilled.	Open point 5.2 fulfilled.
	Open point 5.3: RMS to prepare an addendum with a revised risk assessment for birds and mammals according to the final version of the Guidance	A risk assessment to birds and mammals according to the final version of the Guidance Document on Birds and Mammals for review by the RMS has been provided by the notifier. See BCS **position paper 5_3** (Nicolaus, B.,	May 2005: Revised risk assessment for birds and mammals according to the final version of the Guidance Document on Birds and Mammals has been made. See addendum of May 2005.	Open point 5.3 fulfilled. New Open point 5.12: RMS to amend list of endpoint with respect to the Mammalian repro LOEC of 350 mg a.s./kg diet (26.2

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the evaluation group
	Document on Birds and Mammals to be discussed in an expert meeting. This open point was proposed at the EPCO 27 meeting (see reporting table 5(7))	2005; BCS Document no MO-05-006379) and Bowers (2001), MO-03-005295.	Open point fulfilled.	mg a.s./kg bw)
	Open point 5.4: RMS to prepare an addendum with a revised risk assessment regarding bioaccumulation using the BCF-value based on total radioactivity (BCF of 491 L/kg). (see reporting table 5(9))	For the risk assessment on birds and mammals with respect to secondary poisoning and food chain accumulation the notifier considers the BCF for spirodiclofen itself as the most appropriate value to assess the risk posed by the parent compound. Following the OECD testing guideline 305 the BCF_{fish} should be based upon the parent compound in fish despite total radioactive residues are additionally determined. To address the risk of secondary poisoning caused by **metabolites** of spirodiclofen, a BCF of 491 may be taken into account.	May 2005: Revised risk assessment regarding bioaccumulation using the BCF-value on total radioactivity (BCF of 491 L/kg) has been made. See addendum of May 2005. Open point fulfilled.	Open point 5.4 fulfilled.
	Open point 5.5: MS to discuss the setting of the NOEC for mammals in an expert meeting. (see reporting table 5(12)) *continued* Open point 5.5: MS to discuss the setting of the NOEC for mammals in an expert meeting.	BCS supports the argumentation by the RMS (reporting tables 5(22)) that the ecotoxicologically relevant endpoint is 350 ppm.	May 2005: The comment of SLO was: *"Refinement of the NOEC based on the assumption that continuous exposure does not occur is not acceptable. The decline in residue is accounted for at the exposure side and should not be refined on the toxicity side."* The decline in residue is indeed accounted for at the exposure side, but only for a limited period (21 days). In the study there is a continuous	Open point 5.5 fulfilled.

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the evaluation group
	(see reporting table 5(12))		exposure to constant levels of spirodiclofen for 16 weeks. Under a practical scenario involving a seasonal treatment only, continuous exposure for such a long time is very unlikely due to decline of residues.	
	Open point 5.6: RMS to transfer information (avian toxicity) from column 3 of the reporting table to an addendum to be discussed in an expert meeting. (see reporting table 5(19))	An avian reproduction study conducted with Mallard Duck is available, confirming the results on the first species (Bobwhite quail). No effects on reproduction up to the highest tested dose were observed, the no effect level was calculated to be 111 mg/kg b.w./day. (Bowers (2001), MO-03-005295; see attachment).	May 2005: The information from column 3 of the reporting table has been transferred to an addendum. See addendum of May 2005. Open point fulfilled.	Open point 5.6 fulfilled.
5.1	Notifier to address the effects on bee brood (e.g. a field study, labelling). (see reporting table 5(24))	The notifier has proposed an appropriate labelling in order to minimize the risk to bee brood. The comment of the Rapporteur to address, in addition to the restriction on application during flowering crops, also flowering weeds, is accepted by the notifier.	May 2005: To address the risk to bee brood the notifier has proposed an appropriate labelling in order to minimize the risk to bee brood, e.g. no use of the product during flowering of the crop and avoiding that there are flowering weeds present (e.g. by mowing the weeds). See also addendum of May 2005. Data requirement fulfilled.	Data requirement fulfilled (provided labelling is practical)
	Open point 5.7: RMS to transfer information regarding risk to other non-target arthropods from column 3 of the reporting table to an addendum to be discussed in an expert meeting.		May 2005: The information from column 3 of the reporting table has been transferred to an addendum. See addendum of May 2005. Open point fulfilled.	Open point 5.7 fulfilled.

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the evaluation group
	(see reporting table 5(25))			
	Open point 5.8: MS to discuss the risk to NTA in an expert meeting. (see reporting table 5(26))	Spirodiclofen has a unique, novel Mode of Action which is clearly different to that of IGRs (spirodiclofen inhibits lipid biosynthesis but has no effects on chitin biosynthesis). Furthermore the symptoms of poisoning as well as the biological spectrum for spirodiclofen are different to IGRs. Consequently it is also classified differently to IGRs (MoA group 23 vs 15 for IGRs) by IRAC. Therefore the comparison with IGRs is not justified.	May 2005: RMS can agree with the statement provided by the notifier. But even when the compound is considered as an IGR the data requirements have been fulfilled. According to the Escort 2 guidance document testing of IGRs should be conducted with *T. pyri* and one other species (e.g. *Coccinella septempunctata, Orius laevigatus* or *Chrysoperla carnea*). For spirodiclofen testing was done with *T. pyri* and *Chrysoperla carnea*. In these tests not only mortality but also reproduction was evaluated. So, according to the available guidance the appropriate tests are available. Maybe other tests must be developed in which insects are tested by taking up food. See also addendum of May 2005.	Open point 5.8 fulfilled.
5.2	Notifier to submit the new chronic study with fish. (see reporting table 5(35))	A higher tier study on the chronic toxicity of spirodiclofen to fish was conducted simulating exposure conditions that are more realistic to potential entrance into surface water and its behaviour therein (BCS Document No: MO-02-014087, Dorgerloh, M, & Sommer, H., Chronic effects of BAJ 2740 on selected early	May 2005: Notifier has submitted the new chronic study with fish. This study has been evaluated by the RMS. The NOEC is 0.020 mg/L. The results of the study are used for risk assessment. The revised risk assessment is presented in the addendum of May 2005.	Data requirement fulfilled.

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the evaluation group
		life stages of rainbow trout (Oncorhynchus mykiss) under more realistic conditions of exposure) The study has been submitted by BCS on March 9, 2005. A revised assessment of the chronic risk to aquatic organisms is presented in BCS **position paper 5_9** (Nicolaus, B., 2005a; BCS Document no MO-05-006867).	Data requirement fulfilled.	
	Open point 5.9: MS to discuss the chronic risk to aquatic organisms in an expert meeting. (see reporting table 5(35))	A revised assessment of the chronic risk to aquatic organisms is presented in BCS **position paper 5_9** (Nicolaus, B., 2005a; BCS Document no MO-05-006867).	May 2005: A revised chronic risk assessment for aquatic organisms is presented in the addendum of May 2005. Open point fulfilled.	Open point 5.9 fulfilled.
5.3	Notifier to submit summary on endocrine effect on fish to the RMS. This open point was proposed at the EPCO 27 meeting (see reporting table 5(41))	Statement has been submitted by BCS on March 9, 2005.	May 2005: The notifier has submitted a statement regarding the endocrine effect on fish. This is presented in the addendum of May 2005. Data requirement fulfilled.	Data requirement fulfilled. New Open point 5.13: RMS to consider German national assessment of the ELS study using the enol metabolite.

REPORT OF EPCO EXPERT MEETING 28

SPIRODICLOFEN

Rapporteur Member State: The Netherlands

2. Mammalian Toxicology

Specific comments on the active substance in the section are already listed in the relevant reporting table. Comments submitted for this meeting are listed below.

1. Comments submitted for this meeting:

Date	Supplier	File Name
21 February 2005	Germany	Spirodiclofen com01 DE

2. Documents submitted for meeting:

Date	Supplier	File Name
December 2004	RMS/The Netherlands	Spirodiclofen consultation report
04 March 2005	RMS/The Netherlands	Spirodiclofen reporting table rev1-1
June 2005	RMS/The Netherlands	Spirodiclofen addendum vol3 B6 B7
June 2005	RMS/The Netherlands	Spirodiclofen list of essential studies B6 B7
June 2005	RMS/The Netherlands	Spirodiclofen list of end points B6 B7
13 June 2005	RMS/The Netherlands	Spirodiclofen evaluation table rev0-1

3. Documents tabled at the meeting:

Date	Supplier	File Name
None		

The conclusions of the meeting were as follows:

4. **Data on preparations:** The PPP is a suspension concentrate containing 240 g/l spirodiclofen meant to be applied on apple, pear and grapes in both EU North and EU South and on peach, apricot, nectarine, orange and mandarin in EU South.

5. **Classification and labelling:** Spirodiclofen is classified as ‘IRRITANT’ with the associated risk phrase [R43] ‘May cause sensitisation by skin contact’ and [R40] ‘Limited evidence of a carcinogenic effect’.

6. **Recommended restrictions/conditions for use:** -

7. **Reference List:** None

Areas of concern: None identified

Appendix 1: EPCO discussion table: SPIRODICLOFEN

Appendix 2: Evaluation table

Appendix 1: Discussion Table, Spirodiclofen (In)

2. Mammalian Toxicology

No.	Subject	Discussion EPCO Expert Meeting	Conclusions EPCO Expert Meeting
	Open point 2.1: The oral absorption value to be confirmed at an expert meeting. (see reporting table 2(1))	The oral absorption value of 58% proposed by the RMS was considered to be an underestimation as it was derived from levels of radioactivity in the urine 24 hours after test material administration. The experts considered the studies available for deriving the oral absorption value, and concluded that a value of 65% was appropriate, based on urinary excretion in male rats after 48 hours.	A value of 65% was considered appropriate on the basis of radioactivity in urine and tissues in males. Open point closed.
	Open point 2.2: The endocrine disrupting properties of the compound to be discussed at an expert meeting. (see reporting table 2(4))	The experts considered that as spirodiclofen interferes with enzyme function, it can be considered an endocrine disruptor. It was noted that the effect on steroidogenesis was an indirect effect resulting from effects on general biochemical pathways, and that no androgenic or antiandrogenic effects were noted in mechanistic studies. Furthermore, no reproductive toxicity was noted. While decreased spermatogenesis occurred at paternally toxic doses, this had no effect on litter parameters, demonstrating the high functional reserve capacity of this system. The approach of the application of an additional safety factor for actives with endocrine disrupting properties (as with reproductive toxicity) was discussed. However, this was not considered necessary with spirodiclofen, as the derived reference value would be considerably higher than that derived from other adverse effects: i.e. the risk assessment driven by effects not relating to endocrine disruption provided an adequate margin of safety against potential effects resulting from endocrine disruption. The consequences of deciding that an active was an endocrine disruptor were also briefly discussed, and It was noted that this would have no impact on classification.	Spirodiclofen is considered an endocrine disruptor in that it interferes with steroid hormone synthesis. NOAELs were determined in reproduction and chronic studies, together with the mechanistic investigations indicated no additional safety factors were appropriate. Open point closed.

No.	Subject	Discussion EPCO Expert Meeting	Conclusions EPCO Expert Meeting
	Open point 2.3: RMS to present data (evaluated tissue of toxicokinetic studies) in an addendum. To be discussed together with open point 2.1 at an expert meeting. (see reporting table 2(5))	Data presented in addendum	Data presented in Addendum Open point closed (see open point 2.1).
	Open point 2.4: MS to confirm the relevant NOAEL for the short-term studies at an expert meeting. (see reporting table 2(9))	The experts agreed with the opinion of the RMS that the historical control data provided by the notifier on adrenal cortical vacuolisation in rats demonstrated that the incidence in males at the LOAEL previously set in the 14 week rat study was within the historical control range. As a result, the NOAEL from this study was increased to 8.1 mg/kg bw, based on adrenal cortical vacuolisation in females at the next highest dose. It was noted that a number of studies derived NOELs and that no NOAEL was derived. It was concluded that in the 13 week mouse study, the LOAEL was set at the lowest dose tested, 100 ppm (15.3 mg/kg bw). However, as no obvious dose response in the critical effect was apparent between 100 and 1000 ppm, it was considered that the NOAEL was close to 100 ppm. The lowest overall short term NOAEL was considered to be that of 1.45 mg/kg bw derived from the 1 year dog study, and thus was considered appropriate for the derivation of the AOEL.	The RMS increased the NOAEL for the 14 week rat study to 100 ppm (8.1 mg/kg bw) based on adrenal cortical vacuolisation in females. The NOAEL was increased as a result of the historical control data provided by the notifier, which demonstrated that the vacuolisation observed in males at the next highest dose level was within the historical control range. The lowest overall short term NOAEL was considered to be that of 1.45 mg/kg bw (50 ppm) from the 1 year dog study and appropriate for the derivation of the AOEL Open point closed.

No.	Subject	Discussion EPCO Expert Meeting	Conclusions EPCO Expert Meeting
	Open point 2.5: The genotoxicity to be discussed at an expert meeting. (see reporting table 2(10))	As indicated by the RMS, the increased mutation frequency in the HPRT assay was not confirmed in the parallel culture or in the second trail and is therefore not considered biologically relevant. It was noted that spirodiclofen did not induce micronuclei in the in vivo micronucleus assay, an assay which covers all chromosomal aberrations, at doses at which effects on the bone marrow were demonstrated. It was therefore considered that spirodiclofen had no genotoxic potential, and that no further testing was necessary.	The meeting agreed with the opinion of the RMS that spirodiclofen had no genotoxic potential and that a further in vivo study was not necessary. Open point closed.
	Open point 2.6: MS to confirm the relevant NOAEL for the long-term studies at an expert meeting. (see reporting table 2(11))	The meeting discussed the NOAELs from the long term studies and their use in the derivation of the ADI, and concluded that the 1 year dog study was the most appropriate. The NOAEL from this study was lower than that from the rat carcinogenicity study. Additionally, while no NOAEL was derived from the mouse carcinogenicity study (the LOAEL was 4.1 mg/kg bw), the application of an additional safety factor as a result of the extrapolation from a LOAEL to a NOAEL would result in a similar value to that obtained from the 1 year dog study.	The experts concluded that the relevant NOAEL for the long-term exposures (ADI) was confirmed as 1.45 mg/kg bw derived from the 1 year dog study. It was noted that a similar value for reference doses would be derived using the LOAEL of 4.1 mg/kg bw/day from the mouse study, which would require the use of an additional safety factor for extrapolation from a LOAEL to a NOAEL. The NOAEL in the 2 year rat is 6 mg/kg bw/day. Open point closed.

No.	Subject	Discussion EPCO Expert Meeting	Conclusions EPCO Expert Meeting
	Open point 2.7: MS to confirm the relevant NOAEL for the reproduction toxicity studies at an expert meeting. (see reporting table 2(12))	It was noted that while no NOAEL was derived for parental effects, the effects observed at the LOAEL were minor, and were general systemic effects consistent with those seen in other studies. It was additionally noted that if the LOAEL was used and an additional safety factor applied, that a similar reference value would be derived from the reproductive effects: i.e. a sufficient margin of safety existed.	The experts concluded that the proposed NOAEL for the reproduction toxicity studies was appropriate. It was noted that no NOAEL for parental effects was derived. However, effects noted were consistent with those seen in general toxicity studies. Open point closed.
	Open point 2.8: The carcinogenic effects to be discussed at an expert meeting. (see reporting table 2(13))	It was noted that while tumours were observed, these were observed at doses considerably higher than the NOAEL in the carcinogenicity studies, and that clear NOAELs for carcinogenicity were demonstrated. There was thus considered to be an appropriate margin of safety in the derivation of reference values from lower dose effects not related to carcinogenicity. The experts considered classification as R40 appropriate.	Carcinogenic effects were confirmed at high dose levels, but clear NOAELs were demonstrated. Classification with R40 was supported. Open point closed.
	Open point 2.9: MS to confirm the ADI at an expert meeting. (see reporting table 2(14))	See open point 2.6.	The ADI of 0.015 mg/kg bw confirmed by experts based on the 1 year dog study with a 100 fold factor. Open point closed.
	Open point 2.10: MS to confirm the AOEL at an expert meeting. (see reporting table 2(15))	The experts confirmed that no NOAEL could be derived for a number of studies and confirmed that the most appropriate study for the derivation of the AOEL was the 1 year dog study.	AOEL of 0.009 mg/kg bw/day confirmed by expects including an of oral absorption correction factor of 0.65 giving an overall factor of 154). Open point closed.

No.	Subject	Discussion EPCO Expert Meeting	Conclusions EPCO Expert Meeting
	Open point 2.11: The dermal absorption value to be confirmed at the expert meeting as well as the scientific value of the rhesus monkey study. (see reporting table 2(17))	Experts expressed concerns relating to both the ethics of conducting dermal absorption studies on monkeys, and the quality of the data. A number of member experts indicated that they would not have accepted the study initially, particularly as there were clear OECD guidelines on both in vivo and in vitro assessment of dermal absorption. The experts discussed the proposed dermal absorption value of 2%. Areas of concern with the monkey study included the fact that levels of radioactivity in the skin and body were not determined, and the level of total radioactivity recovered (92%). The low level of variation in individual animals supported the theory that the 8% of radioactivity lost may have been absorbed, and thus the experts concluded that this should be incorporated into the dermal absorption to give a value of 10%. Experts considered the physical chemical properties of spirodiclofen, and considered that the molecular weight and K_{OW} supported a dermal absorption value of 10%. It was therefore concluded that the dermal absorption be set at a value of 10% based on physicochemical properties and supported by the studies in monkeys. It was additionally noted that no data was available on the dermal absorption potential of the formulation dilution. Therefore a value of 65% was proposed, based on the oral absorption value.	1. The experts discussed the validity of the monkey study and determined a value of 10% for the concentrate based on the physical chemistry properties (kow >5), supported by the monkey. 2. A value of 65% was proposed for the dilution based on the oral absorption value. Open point closed.
	Open point 2.12: The operator exposure to be discussed at an expert meeting. The RMS is asked to present the results of the estimations in relation to the systemic AOEL in the addendum. (see reporting table 2(21))	In light of the increase in dermal absorption values discussed in open point 2.11, the RMS will recalculate operator exposure using the modified dermal absorption value.	Operator exposure to be recalculated. See 2.1. Open point still open.
2.1	Notifier to submit historical control data to make an additional evaluation of the renal cortical vacuolation in males possible. (see reporting table 2(31))	See open point 2.4	Data requirement closed.

No.	Subject	Discussion EPCO Expert Meeting	Conclusions EPCO Expert Meeting
	Open point 2.13: RMS to transfer the information (effects chronic feeding study rats) in column 3 of the reporting table to an addendum to be discussed at an expert meeting. (see reporting table 2(33) and 2(11))		Open point closed.
	Open point 2.14: RMS to consider in a revised DAR/corrigendum DE comments on the additional drinking water limit in the DAR, Vol. 3, B.6.10.6. (see reporting table 2(46))		Open point closed.
	New open point	As spirodiclofen is classified as R40, all rat metabolites (i.e. M1-M16) are considered toxicologically relevant. The soil/water metabolites BAJ 2740-enol, BAJ 2740-ketohydroxy, BAJ-dihydroxy and 2,4-dichlorobenzoic acid were identified as metabolites of potential toxicological concern. BAJ 2740-enol (M01) and 2,4-dichlorobenzoic acid (M16) are rat metabolites, and are thus toxicologically relevant. The RMS is to clarify whether BAJ 2740-enol and BAJ 2740-ketohydroxy are rat metabolites.	Metabolites M01-M16 are toxicologically relevant. The RMS is to clarify whether BAJ 2740-enol and BAJ 2740-ketohydroxy are rat metabolites. Open point still open
	Additional point	The experts discussed the end-points table including the reference doses.	Agreed end-points table was produced.

Appendix 2: Evaluation table

2. Mammalian Toxicology

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
	Section 2 Data requirements: ***1*** Open points: ***14***			Section 2 Data requirements: **-** Open points: ***2*** Data gaps: **-**
	Open point 2.1: The oral absorption value to be confirmed at an expert meeting. (see reporting table 2(1))	The RMS used a correction factor of 0.58 to reflect an allegedly incomplete absorption of spirodiclofen from the gastro-intestinal tract. This value obviously originates from a single dose study (3 mg/kg bw) where renal excretion was ca. 58 % in male rats and 75 % in females. A correction factor of 0.58 is regarded to be over-conservative as it does not include spirodiclofen excreted via bile. In a bile cannulation experiment ca. 12 % of the radioactivity was identified in the bile fluid. This finding and the fact that in a repeated dose study > 70 % of the radioactivity were excreted in the urine of males and females, support an overall correction factor of 0.7.	June 2005: The use of 0.58 for oral absorption is considered worst-case for risk assessment purposes. The value of 0.58 was based on excretion of radiolabel in urine 24 hours after administration of 2 mg/kg bw. However, a longer collection period should have been considered. Within the available studies, data could have been derived after 48 hours, which would have resulted in oral absorption of 0.64 for males and 0.76 for females. These latter data are now included in the endpoint list. For risk assessment purposes, the difference between 0.58 and 0.64 is considered negligible. A systemic AOEL of 0.009 mg/kg bw/day (0.63 mg/day) is calculated instead of an AOEL of 0.008 mg/kg bw/day (0.56 mg/day), and no new occupational risk assessment was performed. The AOEL however, is adapted in the critical	EPCO 28 (27.06. – 01.07.2005): A value of 65% was considered appropriate on the basis of radioactivity in urine and tissues in males. Open point closed.

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
	continued Open point 2.1: The oral absorption value to be confirmed at an expert meeting. (see reporting table 2(1))		endpoint list and addendum Furthermore, indeed data on bile cannulation rats were available. However, in this study the urinary excretion was quite low: following administration of 1 mg 14C-spirodiclofen/kg bw to bile duct cannulated male rats 62.8 % of recovered radioactivity was excreted within 24 h, i.e. 22.8% in urine, 28.7 % in faeces and 11.3 % in bile.	
	Open point 2.2: The endocrine disrupting properties of the compound to be discussed at an expert meeting. (see reporting table 2(4))	An independent scientific evaluation by OpdenKamp, title “The possible endocrine effects of BAJ 2740. A critical evaluation” is available as BCS **position paper 2_2** (van Sittert, N. J., Krüse, J., Groeneveld, C. N., 2002; BCS Document no MO-02-011326).	June 2005: See addendum.	EPCO 28 (27.06. – 01.07.2005): Spirodiclofen is considered an endocrine disruptor in that it interferes with steroid hormone synthesis. NOAELs were determined in reproduction and chronic studies, together with the mechanistic investigations indicated no additional safety factors were appropriate. Open point closed.
	Open point 2.3: RMS to present data (evaluated tissue of toxicokinetic studies) in an addendum. To be discussed together with open point 2.1 at an expert meeting. (see reporting table 2(5)) *continued* Open point 2.3:	Apart from liver, kidney, plasma, gastro-intestinal tract and skin, the following tissues were analysed: erythrocytes, spleen, renal fat, adrenal gland, testes, muscle, bone femur, hear, lung, brain, thyroid gland and carcass (Appendices 18-20, including the footnotes, p. 182-188 of Andersch, I. and Koester, J. (2000a), BCS Report no. MO-00-015111). In total bone femur (including the bone marrow) of male and female rats (single	June 2005: See addendum. Data on all studied tissues is now explicitly mentioned in the text.	EPCO 28 (27.06. – 01.07.2005): Data presented in Addendum Open point closed (see open point 2.1).

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
	RMS to present data (evaluated tissue of toxicokinetic studies) in an addendum. To be discussed together with open point 2.1 at an expert meeting. (see reporting table 2(5))	and repeated oral administration), no radioactivity was detected (p. 183, 185 and 187 of Andersch, I. and Koester, J. (2000a), BCS Report no. MO-00-015111). Radioactivity in testes was 0.003 and 0.0008 µg/g and thus below the limit of quantification (p. 34 of Andersch, I. and Koester, J. (2000a), BCS Report no. MO-00-015111)). Also, no radioactivity was detected in uterus and ovary of female rats and in the adrenal gland and thyroid gland of both male and female rats (p. 182-188 of Andersch, I. and Koester, J. (2000a), BCS Report no. MO-00-015111)).		
	Open point 2.4: MS to confirm the relevant NOAEL for the short-term studies at an expert meeting. (see reporting table 2(9)) *continued* Open point 2.4: MS to confirm the relevant NOAEL for the short-term studies at an expert meeting.	See separate BCS **position paper 2_4** (Diesing, L., 2005)	June 2005: See addendum. Several details were included in the study summaries, and the NOAEL in the 14-w oral study in rats is increased to 8.1 mg/kg bw/d, after evaluation of newly submitted historical data on adrenal vacuolation in males. The lowest NOAEL (1.45 mg/kg bw/d) is found in the 1-year oral toxicity study in dogs.	EPCO 28 (27.06. – 01.07.2005): The RMS increased the NOAEL for the 14 week rat study to 100 ppm (8.1 mg/kg bw) based on adrenal cortical vacuolisation in females. The NOAEL was increased as a result of the historical control data provided by the notifier, which demonstrated that the vacuolisation observed in males at the next highest dose level was within the historical control range. The lowest overall short term NOAEL was considered to be that of 1.45 mg/kg bw (50 ppm) from the 1 year dog study and appropriate for the derivation of the AOEL. Open point closed.

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
	(see reporting table 2(9))			
	Open point 2.5: The genotoxicity to be discussed at an expert meeting. (see reporting table 2(10))	BCS fully supports the RMS response and argumentation in reporting table 2(10). All available studies demonstrate that spirodiclofen has no genotoxic potential.	June 2005: No comments, besides our comments in the reporting table 2 (10): An increased mutation frequency with and without metabolic activation was only observed in one culture and was not confirmed in the parallel treated culture nor in the second trial. Therefore, the observed increase was not considered toxicologically relevant. The performance of a second in vivo genotoxicity study is not considered necessary.	EPCO 28 (27.06. – 01.07.2005): The meeting agreed with the opinion of the RMS that spirodiclofen had no genotoxic potential and that a further in vivo study was not necessary. Open point closed.
	Open point 2.6: MS to confirm the relevant NOAEL for the long-term studies at an expert meeting. (see reporting table 2(11)) *continued* Open point 2.6: MS to confirm the relevant NOAEL for the long-term studies at an expert meeting. (see reporting table 2(11))	See separate BCS **position paper 2_6** (Diesing, L., 2005a)	June 2005: See addendum. Several details were included in the study summaries, and the position paper was evaluated. However, the RMS is of the opinion that the NOAELs do not have to be adapted.	EPCO 28 (27.06. – 01.07.2005): The experts concluded that the relevant NOAEL for the long-term exposures (ADI) was confirmed as 1.45 mg/kg bw derived from the 1 year dog study. It was noted that a similar value for reference doses would be derived using the LOAEL of 4.1 mg/kg bw/day from the mouse study, which would require the use of an additional safety factor for extrapolation from a LOAEL to a NOAEL. The NOAEL in the 2 year rat is 6 mg/kg bw/day. Open point closed.
	Open point 2.7:	See separate BCS **position paper 2_7**	June 2005:	EPCO 28 (27.06. – 01.07.2005):

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
	MS to confirm the relevant NOAEL for the reproduction toxicity studies at an expert meeting. (see reporting table 2(12))	(Diesing, L., 2005b)	See addendum. Several details were included in the study summaries, and the position paper was evaluated. However, the RMS is of the opinion that the NOAELs do not have to be adapted.	The experts concluded that the proposed NOAEL for the reproduction toxicity studies was appropriate. It was noted that no NOAEL for parental effects was derived. However, effects noted were consistent with those seen in general toxicity studies. Open point closed.
	Open point 2.8: The carcinogenic effects to be discussed at an expert meeting. (see reporting table 2(13))	BCS fully supports the RMS response and argumentation in reporting table 2(13). See also separate BCS **position paper 2_2** (van Sittert, N. J., Krüse, J., Groeneveld, C. N., 2002; BCS Document no MO-02-011326).	June 2005: No comments in addition to reporting table (2(12)): From the mechanistic studies it was concluded that the carcinogenic potential by BAJ 2510 should be regarded as a non-genotoxic carcinogenic mechanism, since based on the mechanistic studies, BAJ 2510 interferes with steroid hormone synthesis at the level of general biochemical pathways. See also addendum.	EPCO 28 (27.06. – 01.07.2005): Carcinogenic effects were confirmed at high dose levels, but clear NOAELs were demonstrated. Classification with R40 was supported. Open point closed.
	Open point 2.9: MS to confirm the ADI at an expert meeting. (see reporting table 2(14))	Based on the argumentation provided for open points 2(6) and 2(7), BCS supports an ADI value of 0.015 mg/kg bw/day.	June 2005: No comments in addition to in reporting table (2(14)). It was concluded that spirodiclofen is non-genotoxic, and a non-genotoxic carcinogenic mechanism was proposed based on the mechanistic studies. Therefore, it is considered suitable to establish an ADI. The lowest overall NOAEL for non-neoplastic lesions of 1.45 mg/kg bw/day from a 52 week oral toxicity	EPCO 28 (27.06. – 01.07.2005): The ADI of 0.015 mg/kg bw confirmed by experts based on the 1 year dog study with a 100 fold factor. Open point closed.

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
			study in dogs, was supported by short-term toxicity studies with rat and dog, 18 months oral toxicity study with mice and a 2-generation rat toxicity study with LOAELs ranging from 2.9 to 8.0 mg/kg bw/day. Furthermore, these LOAELs were based on critical effects comparable to those observed in the 52 week oral toxicity study with dogs. As there seems to be no effect of exposure duration, it was considered suitable to use the clear NOAEL of 1.45 mg/kg bw/day for the establishment of the ADI. See also addendum. ADI is set at 0.015 mg/kg bw/d	

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
	Open point 2.10: MS to confirm the AOEL at an expert meeting. (see reporting table 2(15))	The RMS used a correction factor of 0.58 to reflect an allegedly incomplete absorption of spirodiclofen from the gastro-intestinal tract. This value obviously originates from a single dose study (3 mg/kg bw) where renal excretion was ca. 58 % in male rats and 75 % in females. A correction factor of 0.58 is regarded to be over-conservative as it does not include spirodiclofen excreted via bile. In a bile cannulation experiment ca. 12 % of the radioactivity was identified in the bile fluid. This finding and the fact that in a repeated dose study > 70 % of the radioactivity were excreted in the urine of males and females, support an overall correction factor of 0.7. Therefore, BCS proposes an AOEL of 0.01 mg/kg bw/day.	June 2005: See comments on open points 2.1 and 2.4. The lowest NOAEL (1.45 mg/kg bw/d) is found in the 1-year oral toxicity study in dogs. Since this is considered a short-term study, this NOAEL is suitable as a starting point for derivation of the AOEL. See also addendum. AOEL is set at 0.009 mg/kg bw/d.	EPCO 28 (27.06. – 01.07.2005): AOEL of 0.009 mg/kg bw/day confirmed by expects including an of oral absorption correction factor of 0.65 giving an overall factor of 154). Open point closed.

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
	Open point 2.11: The dermal absorption value to be confirmed at the expert meeting as well as the scientific value of the rhesus monkey study. (see reporting table 2(17))	BCS supports the dermal absorption value of approx. 2% as derived from the monkey study. We consider the monkey dermal penetration study as appropriate; it was performed as an EPA requirement for the spirodiclofen registration in USA and was subsequently submitted in EU as well. Monkey studies are explicitly mentioned in the EU Guidance Document on Dermal Absorption (Sanco/222/2000 rev. 6 (2002)), where they are described as giving the closest values to human data. Our data were used without further correction by *in vitro* data. - We cannot follow the UK comment that the use of the monkeys is inappropriate since the monkeys (in contrast to rats) are not sacrificed after the study.	June 2005: See comments in reporting table on 2(17), 2(18), 2(19) and 2(20).	EPCO 28 (27.06. – 01.07.2005): 1. The experts discussed the validity of the monkey study and determined a value of 10% for the concentrate based on the physical chemistry properties (kow >5), supported by the monkey. 2. A value of 65% was proposed for the dilution based on f the oral absorption value. Open point closed.
	Open point 2.12: The operator exposure to be discussed at an expert meeting. The RMS is asked to present the results of the estimations in relation to the systemic AOEL in the addendum. (see reporting table 2(21)) *continued*	See separate BCS **position paper 2_12** (Wicke, H., 2004; BCS Document no MO-05-006760) which is based on BCS´s proposed AOEL of 0.01 mg/kg bw/d, a correction factor of 70% bioavailability and a dermal absorption of 2%.	June 2005: Regarding the comments on the sprayed area (knapsack, UK POEM): the note in the DAR is not correct and should read: 'Assuming a tank volume of 15 L, the treated area will be 0.15-0.45 ha (15 L x 30 operations /1000 or 3000 L/ha)'. This shall be taken into account in a revised DAR.	EPCO 28 (27.06. – 01.07.2005): Operator exposure to be recalculated. See 2.1. Open point still open.

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
	Open point 2.12: The operator exposure to be discussed at an expert meeting. The RMS is asked to present the results of the estimations in relation to the systemic AOEL in the addendum. (see reporting table 2(21))		The RMS is of the opinion that the AOEL, dermal absorption, and exposure values have not changed considerably; therefore no recalculation of the risk assessment was considered necessary at this point.	
2.1	Notifier to submit historical control data to make an additional evaluation of the renal cortical vacuolation in males possible. (see reporting table 2(31))	The historical control data were submitted on March 9, 2005. They show that the incidences of adrenal cortical vacuolation seen at 100 and 500 ppm in male rats are covered by the historical control data.	June 2005: See addendum. The submitted data indicated that the observed adrenal vacuolation in males at the lowest two dose levels (100 and 500 ppm) was within the historical data. Since no historical data for females was presented, the NOAEL was changed to 8.1 mg/kg bw/d, based on adrenal vacuolation in females at 500 ppm and above.	EPCO 28 (27.06. – 01.07.2005): Data requirement closed.
	Open point 2.13: RMS to transfer the information (effects chronic feeding study rats) in column 3 of the reporting table to an addendum to be discussed at an expert meeting. (see reporting table 2(33) and 2(11))	See comments under Open Point 2.6.	June 2005: See addendum. More detailed information on weights of several organs were included, However, the NOAEL of the study was not changed.	EPCO 28 (27.06. – 01.07.2005): Open point closed.
	Open point 2.14:		June 2005:	EPCO 28 (27.06. – 01.07.2005):

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
	RMS to consider in a revised DAR/corrigendum DE comments on the additional drinking water limit in the DAR, Vol. 3, B.6.10.6. (see reporting table 2(46))		The drinking water limit should not exceed the EU drinking water limit for pesticides of 0.1 µg/L and should not be more than 10% of the ADI. Since the EU limit is the lowest of these two, the EU drinking water limit for pesticides of 0.1 µg/L is applicable for spirodiclofen, as indicated in the DAR. We admit that the wording could have been clearer.	Open point closed.
	New open point 2.15: RMS to revise the list of end points according the amendments proposed by EPCO 28.			EPCO 28 (27.06. – 01.07.2005): Open point still open.

REPORT OF EPCO EXPERT MEETING 29

SPIRODICLOFEN

Rapporteur Member State: The Netherlands

Specific comments on the active substance in the section

3. Residues

are already listed in the relevant reporting table. Comments submitted for this meeting are listed below.

1. Comments submitted for this meeting:

Date	Supplier	File Name
21 February 2005	Germany	Spirodiclofen com01 DE

2. Documents submitted for meeting:

Date	Supplier	File Name
December 2004	RMS/The Netherlands	Spirodiclofen consultation report
04 March 2005	RMS/The Netherlands	Spirodiclofen reporting table rev1-1
June 2005	RMS/The Netherlands	Spirodiclofen addendum vol3 B6 B7
June 2005	RMS/The Netherlands	Spirodiclofen list of essential studies B6 B7
June 2005	RMS/The Netherlands	Spirodiclofen list of end points B6 B7
13 June 2005	RMS/The Netherlands	Spirodiclofen evaluation table rev0-1

3. Documents tabled at the meeting:

Date	Supplier	File Name
None.	Name	

The conclusions of the meeting were as follows:

4. **Data on preparations:** Not considered at EPCO 29.

5. **Classification and labelling:** Not considered at EPCO 29.

6. **Recommended restrictions/conditions for use:** Not considered at EPCO 29.

7. **Reference List**

Areas of concern: None

Appendix 1: EPCO discussion table: SPIRODICLOFEN

Appendix 2: Evaluation table

Appendix 1: Discussion Table, Spirodiclofen (In)

3. Residues

No.	Subject	Discussion EPCO Expert Meeting	Conclusions EPCO Expert Meeting
3.1	Notifier to submit a study to show extraction efficiency from method 00568 and storage stability in samples of the grape metabolism study. (see reporting table 3(1))	A study was submitted to demonstrate the extraction efficiency for the method 00568. The meeting discussed that there was a discreprancy with the analysis of the residue levels within the metabolism study and the residue trials. The meeting concluded that the problem was not an analytical problem and was due to variability in results between the trials and the metabolism study (the latter of which is regarded as semi-quantitative).	Data requirement met. The additional data were acceptable and there are no outstanding concerns
3.2	Notifier to submit additional recovery experiments in apple pomace at 1.0 mg/kg spirodiclofen. (see reporting table 3(2))	This additional data was provided and recovery levels at 1.0 mg/kg were sufficient. Lower levels (0.02 to 0.2 mg/kg) had been reported initially and the additional data was requested to ensure validation was sufficient and the performance of the analytical methodology suitable for the results determined. The meeting concluded that this additional data was acceptable.	Data requirement met. The additional data were acceptable and there are no outstanding concerns

No.	Subject	Discussion EPCO Expert Meeting	Conclusions EPCO Expert Meeting
	Open point 3.2: RMS to present MRL calculation for pome fruit from southern uses in an addendum taken into account the information given in column 3 of the reporting table. (see reporting table 3(4))	A new calculation as presented in the addendum was highlighted for pome fruit to address trials from the North and trials from the South in the MRL calculation. The meeting agreed the new assessment concluding that for the combined data set the results were comparable across North and Southern Europe and therefore the whole dataset could be used to propose the MRL.	Open point 3.2: Open point fulfilled. New presentation supports the same MRL proposal.
	Open point 3.3: MS to discuss in an expert meeting the issues raised by a fat soluble parent and a metabolite which is not fat soluble to try and resolve this potential difficulty for monitoring. Depending on the outcome of the residue expert meeting, it could be necessary for the phys-chem experts to require further data with respect to an enforcement method for food of animal origin. (see reporting table 3(5))	The meeting discussed the metabolism in lactating goats study. This study indicated that no parent compound was detected with the metabolite M01 being detected at the highest levels (> 80%TRR) in all matrices (study conducted at >600N rate). The meeting confirmed that the metabolite M01 is not fat soluble whereas parent compound is based on the logPow. In addition the total residue found in fat was only 0.14 mg/kg in the metabolism study. The metabolism study pointed to a single compound only as suitable for the residue definition (M01 only). The feeding study in lactating cows was conducted at 1x, 3x and 10x dose. The metabolite M01 was not detected in milk or any of the tissue matrices except for kidney from the 10x dose study. At the 3x feeding levels no parent and no metabolite M01 were found in cream, kidney and fat matrices. At 10 x a mean residue of 0.06 mg/kg M01 was found in kidney. In the fat and cream at 10 x very low level residues of up to 0.012 mg/kg of parent were observed. However given the information from the metabolism study, and the exaggerated rate (10x) at which the residues were observed in the feeding study dosed on each day for 29 days, the meeting agreed that for monitoring purposes a residue definition of metabolite M01 only is appropriate. The uses considered in the DAR do not give rise to significant residue in animal products and the meeting agreed that the residue definition for risk assessment purposes should also be metabolite M01 only based on the supported uses. If the use is extended to other crops fed to animals and the animal intakes significantly increase then the residue definition will need to be re-considered at a MS level. The meeting agreed with the RMS proposal. The residue definitions for monitoring purposes is confirmed to EPCO 30 via a table of residue definitions and MRL proposals that was passed to them prior to their meeting.	Open point 3.3 Open point fulfilled. The meeting agreed the RMS proposal for the residue definition for risk assessment and monitoring purposes to include metabolite M01 only. If the use is extended to other crops fed to animals, if animal intakes are significantly increased then the residue definition would need to be re-considered. EPCO 30 were informed of the monitoring residue definition.

No.	Subject	Discussion EPCO Expert Meeting	Conclusions EPCO Expert Meeting
3.3	Notifier to submit the following study reports for evaluation: - Krolski, M.E. 2000. BAJ 2740 240 SC. Magnitude of the residue in orange processed commodities. Bayer AG Div Report No. 109726. - De Haan, R.A. 2000. BAJ 2740 240 SC. Magnitude of the residue in apple processed commodities. Bayer AG Div Report No. 110025. (see reporting table 3(7))	These studies were provided and the methods analyse for spirodiclofen compound only and not for the metabolite M01 which is expected to be formed over processing that involves heating. The meeting concluded that these studies could therefore not be relied upon to propose processing factors.	Data requirement has been met. The studies have been submitted and evaluated. As parent only was analysed rather than also including the relevant metabolite M01 these studies have not been used to propose processing factors (studies not relied upon).
3.4	Notifer to provide more validation data for the method 109 720 for the determination of residues in food of animal origin. (see reporting table 1(17))	This method was used in the livestock feeding studies and there were insufficient recoveries shown for the residues when taking account of the validation data in the methods of analyses reports. The meeting agreed that sufficient recovery information was available when all the data together from the livestock feeding studies was considered. The meeting agreed that the method was sufficiently validated for the purpose of the study (feeding study) and the data requirement was met.	Data requirement met. All the available validation data combined support the view that the method of analysis used in the feeding study has been sufficiently validated.

No.	Subject	Discussion EPCO Expert Meeting	Conclusions EPCO Expert Meeting
	End points – animal products	The end-points were discussed, particularly with regard to animal product residues. The DAR does not state the results for the 1x dose level, although the residue levels are expected to be low. The RMS will consider this further.	New open point 3.4: RMS to check the residue levels at 1x dose rate in the lactating cow feeding study and to up date the end points to reflect the metabolite M01. Further consideration will need to be given as to whether there will be a need to set MRLs for animal products.
	End-points and list of essential studies	A list of essential studies was submitted for the meeting	New open point 3.5: RMS to update endpoints to reflect the discussion of the meeting.

Appendix 2: Evaluation table

3. Residues

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
	Section 3 Data requirements: ***4*** Open points: ***3***			Section 3 Data requirements: ***0*** Open points: ***2***
3.1	Notifier to submit a study to show extraction efficiency from method 00568 and storage stability in samples of the grape metabolism study. (see reporting table 3(1))	A study to address this point (Report No. MEF-04/453 (MO-04-013634)) was submitted on March 9, 2005. The extraction efficiency of residue method 00568 was 93 %. Re-analysis of a grape sample that had been stored for 7 years at -20 °C yielded a BAJ 2740 residue of 1.70 mg/kg, compared to 1.80 mg/kg for the original analysis. Thus, the recovery is 93 %, demonstrating that residues of BAJ 2740 are stable for at least 7 years at -20 °C.	June 2005: Report: Extraction efficiency testing of the residue method for the determination of BAJ2740 in grapes using aged radioactive residue - which is summarised in the addendum - shows that extractability of aged radioactive residue is 93%. Data requirement considered fulfilled.	EPCO 30/06/2005 Data requirement is met. The additional data were acceptable and there are no outstanding concerns
3.2	Notifier to submit additional recovery experiments in apple pomace at 1.0 mg/kg spirodiclofen. (see reporting table 3(2))	The study (Zimmer and Gnielka, 2005, MO-04-013344) was submitted on March 9, 2005. The report describes the successful validation of the method at 1 mg/kg in apple pomace.	June 2005: Report: Addendum 01 to report no. MR-351/99: Validation of the residue analytical method 00568 for the determination of BAJ 2740 in plant materials by LC-MS/MS - which is summarised in the addendum - shows that recoveries of spirodiclofen in apple pomace at 1.0 mg/kg is 94 ± 3.1%	EPCO 30/06/2005 Data requirement is met. The additional data were acceptable and there are no outstanding concerns

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
			Data requirement considered fulfilled.	
	Open point 3.2: RMS to present MRL calculation for pome fruit from southern uses in an addendu taken into account the information given in column 3 of the reporting table. (see reporting table 3(4))	Notifier agrees with the proposal of the rapporteur (see reporting tables 3(4))	June 2005: Addressed in addendum. Open point considered closed.	EPCO 30/06/2005 Open point 3.2: Open point fulfilled. New presentation supports the same MRL proposal.
	Open point 3.3: MS to discuss in an expert meeting the issues raised by a fat soluble parent and a metabolite which is not fat soluble to try and resolve this potential difficulty for monitoring. Depending on the outcome of the residue expert meeting, it could be necessary for the phys-chem experts to require further data with respect to an enforcement method for food of animal origin. (see reporting table 3(5))	See open point 1.2: A new method for enforcement of animal matrices (muscle, milk, liver, fat) for parent and BAJ 2740-enol was developed and is submitted together with the evaluation tables: Zimmer (2005), MO-05-005229 (ILV: Bacher (2005), MO-05-005724)	June 2005: No comment.	EPCO 30/06/2005 Open point 3.3 Open point fulfilled. The meeting agreed the RMS proposal for the residue definition for risk assessment and monitoring purposes to include metabolite M01 only. If the use is extended to other crops fed to animals, if animal intakes are significantly increased then the residue definition would need to be re-considered. EPCO 30 were informed of the monitoring residue definition.

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
3.3	Notifier to submit the following study reports for evaluation: - Krolski, M.E. 2000. BAJ 2740 240 SC. Magnitude of the residue in orange processed commodities. Bayer AG Div Report No. 109726. - De Haan, R.A. 2000. BAJ 2740 240 SC. Magnitude of the residue in apple processed commodities. Bayer AG Div Report No. 110025. (see reporting table 3(7))	Both reports were submitted on March 9, 2005; the corresponding analytical method (Moore et al. (2002), MO-02-005920) is submitted together with these comments (see attachments).	June 2005: Studies reports provide and evaluated in the addendum. Report No. 110025 is not of author De Haan but Harbin, AM. As only parent spirodiclofen was measured, and degradation into M01 takes place (toxicological relevant) during heating at a large extend, and due to inconsistencies in results of apple processing studies, it is concluded that no processing factors should be proposed. Data requirement considered fulfilled.	EPCO 30/06/2005 Data requirement has been met. The studies have been submitted and evaluated. As parent only was analysed rather than also including the relevant metabolite M01 these studies have not been used to propose processing factors (studies not relied upon).
3.4	Notifer to provide more validation data for the method 109 720 for the determination of residues in food of animal origin. (see reporting table 1(17)) *continued*	A statement was submitted on March 9, 2005, to show that the animal method 109720 used in the feeding study is sufficiently validated. Additional validations are available from the ILV (Nelson, S; Hoshowski, J. (2001), MO-02-017505, see attachments) and as concurrent recoveries from the feeding study.	June 2005 Notifier provided a statement, consisting of recovery data from the original report describing the analysis method, the ILV-report and the livestock feeding study. Although the number of recoveries is variable for the different matrices and metabolites (i.e parent or M01), al least 3 recoveries are assayed per level (LOQ and 10*LOQ) and at least 8 samples per matrix are tested. Except from M01 in milk at the lowest level (0.002 mg/kg: 143 ± 28%, n=3, however overall recovery for M01 in milk = 111 ± 18.4%) all calculations	EPCO 30/06/2005 Data requirement met. All the available validation data combined support the view that the method of analysis used in the feeding study has been sufficiently validated.

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
	Notifer to provide more validation data for the method 109 720 for the determination of residues in food of animal origin. (see reporting table 1(17))		show recoveries between 82-112% with relative standard deviations < 19.3% RMS is of the opinion that the method is validated well for the underlying goal (i.e. evaluation of the feeding study in cow) Data requirement considered fulfilled.	
	New open point 3.4: RMS to check the residue levels at 1x dose rate in the lactating cow feeding study and to up date the end points to reflect the metabolite M01. Further consideration will need to be given as to whether there will be a need to set MRLs for animal products.			EPCO 30/06/2005 Point still open
	New open point 3.5: RMS to update endpoints and list of essential studies to reflect the discussion of the meeting.			EPCO 30/06/2005 Point still open

Report of EPCO Expert Meeting 30

SPIRODICLOFEN

Rapporteur Member State: The Netherlands

Specific comments on the active substance in the section

1. Physical and Chemical Properties

are already listed in the relevant reporting table. Comments submitted for this meeting are listed below.

1. Comments submitted for this meeting:

None

2. Documents submitted for meeting:

Date	Supplier	File Name
December 2004	RMS/The Netherlands	Spirodiclofen consultation report
04 March 2005	RMS/The Netherlands	Spirodiclofen reporting table rev1-1
June 2005	RMS/The Netherlands	Spirodiclofen addendum vol4
June 2005	RMS/The Netherlands	Spirodiclofen addendum vol3 B2 B5
June 2005	RMS/The Netherlands	Spirodiclofen list of essential studies B1-B3 B5
June 2005	RMS/The Netherlands	Spirodiclofen list of end points B1-B3 B5
27 June 2005	RMS/The Netherlands	Spirodiclofen evaluation table rev0-1

3. Documents tabled at the meeting:

None

The conclusions of the meeting were as follows:

4. Data on preparations: BAJ 2740 SC 240

5. Classification and labelling: Not discussed

6. Recommended restrictions/conditions for use: None

7. Reference List: Yes

Areas of concern: None

Appendix 1: EPCO discussion table: SPIRODICLOFEN

Appendix 2: Evaluation table

Appendix 1: Discussion Table, Spirodiclofen (In)

1. Physical and Chemical Properties

No.	Subject	Discussion EPCO Expert Meeting	Conclusions EPCO Expert Meeting
1.1	Notifier to submit details of the GC headspace method of analysis for the impurity 5. (see reporting table 1(1))	Details given in addendum to vol 4.	Data requirement fulfilled
	Open point 1.1: RMS to amend the list of endpoints (list of representative uses) regarding the product name (code number). (see reporting table 1(5))	Still open. RMS to amend end-points	Open point remains open

No.	Subject	Discussion EPCO Expert Meeting	Conclusions EPCO Expert Meeting
1.2	Notifier to submit: 1. A 5 batch analysis of the large scale production; 2. For the compound which is analysed with GC-FID, a confirmatory method using specific detectors with the same method (e.g. GC-MS) or data to confirm the identity of the impurities revealed by chemical analysis must be provided to address the requirement of the Directive on the specificity of the method(s). (see reporting table 1(12))	New data submitted, along with methods of analysis and validation data for HPLC-DAD. Summarised in addendum to vol 4, with comparison to old data. Slight shortening of the pathway due to two starting materials being commercially available (no purities provided for two new materials) Data requirement: Notifier to provide purity of two new starting materials. Bridging statement to justify slight change in specification, which is to be considered by tox and ecotox. Mamtox & Ecotox to confirm that new specification from full-scale production is acceptable. Note from EFSA: in future if changes made to method of manufacture, highlight changes from original method in reaction scheme by crossing out obsolete steps. Fulfilled	Data requirement fulfilled Data gap: Notifier to provide purity of two new starting materials. Message for Mamtox & Ecotox to confirm that new specification from full-scale production is acceptable

No.	Subject	Discussion EPCO Expert Meeting	Conclusions EPCO Expert Meeting
	Note: Depending on the outcome of the residue expert meeting [see open point 3.3], it could be necessary to require further data with respect to an enforcement method for food of animal origin. (see reporting table 1(17))	Metabolite M01 (spirodiclofen-enol) is residue of concern. New method for enforcement of animal matrices has been submitted and evaluated. List of end-points has been updated accordingly. asterisks in table 5.2.8 of B5 addendum are of no consequence. Fulfilled	Fulfilled
	Open point 1.2: Being aware that a data requirement is set for large scale batch analysis, this is not comprehensible from the list of endpoints. Therefore, it should be indicated that the minimum purity given in the list of endpoints is related to a pilot plant. (see reporting table 1(44))	Over-ruled by large scale production. Certified limit of a.s. content is higher than from pilot plant scale and has been amended in the end-points.	Open point fulfilled

No.	Subject	Discussion EPCO Expert Meeting	Conclusions EPCO Expert Meeting
	Open point 1.3: RMS to confirm the residue definitions for monitoring for soil and water. Depending on the outcome of the expert meetings (fate and behaviour, ecotoxicology and toxicology) further data could be required. (see reporting table 1(45))	Further clarification required from toxicology and ecotox to confirm monitoring residue definition for water and soil unfulfilled	Open point remains open Message to toxicology and ecotoxicology section: To confirm monitoring residue definition for water and soil
1.3	Notifier to submit solubility in water and partition co-efficient data at pH 7. (see reporting table 1(51))	Studies submitted and evaluated in addendum to volume 3 End-points amended accordingly Fulfilled	Data requirement fulfilled

No.	Subject	Discussion EPCO Expert Meeting	Conclusions EPCO Expert Meeting
	Open point 1.4: MS to discuss in an expert meeting as a general point whether it is acceptable to address both annex points on oxidising properties (for the active substance and the formulation) only with justifications based on a theoretical assessment. (see reporting table 1(53))	Done in EPCO 25; concluded that this was acceptable. See also EFSA working document for EPCO expert meetings (Section 1) Fulfilled	Open point fulfilled
	Additional comments on end points	Purities missing from the list of end-points RMS to confirm availability of purities	New open point to confirm purities in end points

Appendix 2: Evaluation table

1. Identity, Physical and chemical properties, Details of uses and further information, Methods of analysis

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
	Section 1 Data requirements: ***3*** Open points: ***4***			Section 1 Data requirements: **-** Open points: ***2*** Data gaps: ***1***
1.1	Notifier to submit details of the GC headspace method of analysis for the impurity 5. (see reporting table 1(1))	Impurity 5 is analysed by Method 2005-0013102-02; Kraemer, F.; Date 2002-10-18; BCS Report No, Mo-02-016109. The validation report is "Validation Report for Method 2005-0013102-02 VB1.4-[redacted]", Kraemer, F.; date 2002-11-05; BCS Report no. MO-02-017600. Both studies were submitted on March 9, 2005.	June 2005: Details of the GC headspace method of the analysis for the impurity 5 ([redacted]) are given. Method: see Kraemer, F.; MO-02-016109 Validation: see Kraemer F.; MO-02-017600	EPCO 30 (05. – 07.07.2005): Data requirement fulfilled
	Open point 1.1: RMS to amend the list of endpoints (list of representative uses) regarding the product name (code number). (see reporting table 1(5))		June 2005: List of endpoints has been amended.	EPCO 30 (05. – 07.07.2005): Open point still open

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
1.2	Notifier to submit: 1. A 5 batch analysis of the large scale production; 2. For the compound which is analysed with GC-FID, a confirmatory method using specific detectors with the same method (e.g. GC-MS) or data to confirm the identity of the impurities revealed by chemical analysis must be provided to address the requirement of the Directive on the specificity of the method(s). (see reporting table 1(12))	The new 5 batch analysis of the large scale production is described in Rüngeler, W., 2004-09-15; BCS Report No. MO-04-009359 in connection with the corresponding analytical methods and validation reports. The 5 batch analysis also contains the confirmatory methods mentioned in the data requirement. A bridging statement explaining and justifying the new specification (P. Linke-Ritzer, L. Diesing, C. Maus, 2005-02-01, BCS Report No. MO-05-004882; including references) was also submitted. The MA study, the bridging statement, and all references were submitted on March 9, 2005.	June 2005: A 5-batch analysis of the large scale production has been submitted. Including the analytical methods and validation data of all (specified) impurities. The compound which is analysed with GC-FID in the 5-batch analysis of the pilot plant batches, is in the new 5-batch analysis analysed with HPLC, identity is confirmed by UV-spectrum comparison. The large scale production pathway is shortened as two intermediates are commercially available. Purity of the commercially available intermediates [redacted] and [redacted] are not submitted. A bridging statement explaining and justifying the new specification was also submitted. This should be evaluated by (eco)tox.	EPCO 30 (05. – 07.07.2005): Data requirement fulfilled. Data gap 1.4 identified.
1.4	Notifier to provide purity of two new starting materials. This data gap was indentified at the EPCO 30 meeting			EPCO 30 (05. – 07.07.2005): Data gap identified.

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
	Message from EPCO 30 to experts of the sections ecotoxicology and mammalian toxicology: To confirm that new specification from full-scale production is acceptable			
	Note: Depending on the outcome of the residue expert meeting [see open point 3.3], it could be necessary to require further data with respect to an enforcement method for food of animal origin. (see reporting table 1(17))	A new method for enforcement of animal matrices (muscle, milk, liver, fat) for parent and BAJ 2740-enol was developed and is submitted together with the evaluation tables: Zimmer (2005), MO-05-005229 (ILV: Bacher (2005), MO-05-005724)	June 2005: For animal products spirodiclofen-enol is the residue of concern. An enforcement method to determine spirodiclofen-enol (M01) in cattle products (meat, milk, kidney, liver, fat) should be provided, since deuterated internal standards are not commonly available (Method 109720, see B.5.2.4 in the monograph) and implementation in an multiresidue method was not tested (Enforcement method 00086/M030 [extended revision of DFG Method S19], see B.5.2.1 in the monograph). A new method (Zimmer (2005) MO-05-005229) for enforcement of animal matrices (muscle, milk, liver, fat) for parent and BAJ 2740-enol and an ILV (Bacher (2005), MO-05-005724) are submitted. List of endpoints has been amended.	EPCO 30 (05. – 07.07.2005): Fulfilled

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
	Open point 1.2: Being aware that a data requirement is set for large scale batch analysis, this is not comprehensible from the list of endpoints. Therefore, it should be indicated that the minimum purity given in the list of endpoints is related to a pilot plant. (see reporting table 1(44))	The minimum purity of 95.5% which is currently given in the list of endpoints refers to a pilot plant production scale. According to the new MA-study (large scale production) the minimum purity is increased to 96.5%.	June 2005: The large-scale production leads to a technical product of higher purity than the pilot plant material. Therefore the certified limit of the active substance was increased from 955 g/kg to 965 g/kg. This has also been amended in the list of endpoints.	EPCO 30 (05. – 07.07.2005): Open point fulfilled
	Open point 1.3: RMS to confirm the residue definitions for monitoring for soil and water. Depending on the outcome of the expert meetings (fate and behaviour, ecotoxicology and toxicology) further data could be required. (see reporting table 1(45)) *continued* Open point 1.3:	The open point under 1(45) in the reporting table covers two different aspects: a) the question about the residue definition in soil and water and b) the question about the relevance of an impurity. a) residue definition in soil and water: The residue definition for water includes the parent compound and BAJ 2740-enol, which is a major hydrolysis product. Concerning a separate residue definition for ground water, see Open point 4(3). The residue definition for soil as given in the DAR should only include the parent compound and BAJ 2740-enol. All other metabolites are ecotoxicologically not relevant – See also BCS **position paper 1_3a** (Kaune, A., Maus, C., 2005; BCS Document no MO-05-006082).	June 2005: The residue definition for water and soil includes the parent compound and BAJ 2740-enol. BAJ 2740-Enol is an impurity in technical spirodiclofen, which has to be categorised as significant because of its concentration in the technical active substance. However, due to its toxicological and ecotoxicological properties it is not a relevant impurity.	EPCO 30 (05. – 07.07.2005): Open point still open.

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
	RMS to confirm the residue definitions for monitoring for soil and water. Depending on the outcome of the expert meetings (fate and behaviour, ecotoxicology and toxicology) further data could be required. (see reporting table 1(45))	b) relevant impurities: In reporting table 1(45) EFSA additionally raises the question about the relevance of an impurity in the technical material. Please see Bayer CropScience **position paper 1_3b** (Linke-Ritzer, P., Nicolaus, B., 2005; BCS Document no MO-05-006689).		
1.3	Notifier to submit solubility in water and partition co-efficient data at pH 7. (see reporting table 1(51))	The studies have been started; the reports are not finalised yet and will be submitted as soon as possible. The report numbers, the titles and the preliminary results are: Report No.: PA05/027 Title: Spirodiclofen, BAJ 2740 (AE 1344097) Water Solubility at pH 7 Result: Solubility in water at 20°C: cs = 0.19 mg / L = 190 µg / L Report No.: PA05/028 Title: Spirodiclofen, BAJ 2740 (AE 1344097) Partition Coefficient 1-Octanol / Water at pH 7 Result: log Pow = 5.1	June 2005: The notifier submitted studies of the water solubility and partition co-efficient of spirodiclofen at pH 7, which full-fill data requirement 1.3. List of endpoints has been amended.	EPCO 30 (05. – 07.07.2005): Data requirement fulfilled

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
	Open point 1.4: MS to discuss in an expert meeting as a general point whether it is acceptable to address both annex points on oxidising properties (for the active substance and the formulation) only with justifications based on a theoretical assessment. (see reporting table 1(53))		June 2005: According to expert meeting (EPCO 25), it is acceptable to address both annex points on oxidising properties (for the active substance and the formulation) only with justifications based on a theoretical assessment.	EPCO 30 (05. – 07.07.2005): Open point fulfilled

Summary of representative uses evaluated (spirodiclofen)[1]

Crop and/ or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks (m)
					Type (d-f)	Conc. of as (i)	method kind (g-h)	growth stage & season (j)	number max (k)	interval between applications	kg as/hL max	water L/ha max	kg as/ha max		
Apple (MABSD) **Pear** (PYUCO)	EU North	not yet deter-mined	F	mites and sucking insects	SC	240 g/L	overall spray	BBCH 51 – 57 **or** 69 - 85	1	n.a.	0.0096	1500	0.144	14	
Grape (VITVI)	EU North	not yet deter-mined	F	mites	SC	240 g/L	overall spray	BBCH 03 – 57 **or** 69 - 85	1	n.a.	0.0096	1000	0.096	14	
Apple (MABSD) **Pear** (PYUCO)	EU South	not yet deter-mined	F	mites and sucking insects	SC	240 g/L	overall spray	BBCH 51 – 57 **or** 69 - 85	1	n.a.	0.0096	1500	0.144	14	
Peach (PRNPS) **Apricot** (PRNAR) **Nectarine** (PRNPN)	EU South	not yet deter-mined	F	mites	SC	240 g/L	overall spray	BBCH 69 – 85	1	n.a.	0.0096	1500	0.144	14	
Orange (CIDSI) **Mandarin** (CIDRE)	EU South	not yet deter-mined	F	mites	SC	240 g/L	overall spray	BBCH 69 – 85	1	n.a.	0.0048	3000	0.144	14	

[1] Uses for which the risk assessment can not be concluded are marked grey.

Crop and/ or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks (m)
					Type (d-f)	Conc. of as (i)	method kind (g-h)	growth stage & season (j)	number max (k)	interval between applications	kg as/hL max	water L/ha max	kg as/ha max		
Grape (VITVI)	EU South	not yet deter-mined	F	mites	SC	240 g/L	overall spray	BBCH 03 – 57 **or** 69 - 85	1	n.a.	0.0096	1000	0.096	14	

(a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)
(b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
(f) All abbreviations used must be explained
(g) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plant - type of equipment used must be indicated
(i) g/kg or g/l
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) Indicate the minimum and maximum number of application possible under practical conditions
(l) PHI - minimum pre-harvest interval
(m) Remarks may include: Extent of use/economic importance/restrictions

REPORT OF PRAPeR EXPERT MEETING 66

SPIRODICLOFEN

Rapporteur Member State: NL

Specific comments on the active substance in the section

1. Physical and Chemical Properties

are already listed in the relevant reporting table. Comments submitted for this meeting are listed below.

1. Comments submitted for this meeting:

Date	**Supplier**	**File Name**
none		

2. Documents submitted for meeting:

Date	**Supplier**	**File Name**
April 2009	NL	spirodiclofen_addendum_B2_B5_June05_revised April 2009.doc
April 2009	NL	spirodiclofen_addendum_Vol4_revised April 2009_cover page.doc
April 2009	NL	spirodiclofen_essential studies_September 2006_revised April 2009.doc
April 2009	NL	spirodiclofen_evaluation table rev 3-0_revised April 2009
April 2009	NL	spirodiclofen_list of endpoints_revised April 2009.doc
04-03-2005	NL	Spirodiclofen_reporting_table_rev1-1_(04-03-2005).doc

3. Documents tabled at the meeting:

Date	**Supplier**	**File Name**
none		

The conclusions of the meeting were as follows:

4. **Data on preparations:** Envidor SC 240

5. **Classification and labelling:** not discussed

8. Recommended restrictions/conditions for use: none

9. Reference list: Not discussed

Areas of concern: none

Appendix 1: Discussion table: SPIRODICLOFEN

Appendix 2: Evaluation table

Appendix 1: Discussion Table, Spirodiclofen (In)

1. Physical and Chemical Properties

No.	Subject	Discussion Expert Meeting	Conclusions Expert Meeting
1.5	Data requirement proposed at the evaluation meeting: <u>Evaluation Meeting (04.-06-12.2006):</u> As the impurities 3-(2,4-dichlorophenyl)-4-hydroxy-1-oxaspiro[4.5]dec-3-en-2-one (BAJ-2740 enol) and N,N-dimethylacetamide are consider relevant storage stability data where the impurities are analysed for in the PPP before and after storage is missing. Data requirement open.	Accelerated storage study available, stable. The Meeting agreed that it is unlikely that these impurities are formed during storage of the PPP and a shelf life study is not required.	Data requirement closed
1.6	Data requirement proposed at the evaluation meeting: <u>Evaluation Meeting (04.-06-12.2006):</u> As the impurities 3-(2,4-dichlorophenyl)-4-	Methods provided by the notifier in revised Addendum Method was accepted by RMS. Method should be described in Vol 3 and not in 4. L	Data requirement closed New open point: Method for relevant impurities to be transferred to Vol 3 New open Point EFSA: Check whether the methods are appropriate

No.	Subject	Discussion Expert Meeting	Conclusions Expert Meeting
	hydroxy-1-oxaspiro[4.5]dec-3-en-2-one (BAJ-2740 enol) and N,N-dimethylacetamide are consider relevant validated methods of analysis for these compounds in the PPP are missing. Data requirement open.		for the maximum levels of the impurities set following the Tox meeting.
	New open point 1.5: Method for relevant impurities to be transferred to Vol 3		Open point open
	New open Point 1.6: EFSA:to check whether the methods are appropriate for the maximum levels of the impurities set following the Tox meeting.		Open point open
1.7	Data requirement proposed at the evaluation meeting: <u>Evaluation Meeting (04.-06-12.2006):</u> As the impurities 3-(2,4-dichlorophenyl)-4-hydroxy-1-oxaspiro[4.5]dec-3-en-2-one (BAJ-2740 enol) and N,N-	Spectra provided in revised Addendum April 2009 and found to be accaptable	Data requirement closed

No.	Subject	Discussion Expert Meeting	Conclusions Expert Meeting
	dimethylacetamide are consider relevant spectra are missing. Data requirement open.		
	List of end points	Use the new agreed template Maximum levels for relevant impurities should be included when agreed by tox Classification points: purity should be given Relevant impurity methods should be moved to the box PPP (principle of method) Detection method should be provided together with separation technique List of representative uses: check the remark footnotes after tox meeting The dissociation constant should be verified given that at pH 7 the active is stable	Open point: The list of end points should be amended in accordance with the report of PRAPeR 66.
	New open point 1.7: RMS to amend the list of end points according to the discussions during thef PRAPeR 66 meeting.		Open point open

Appendix 2: Evaluation table

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO and PRAPeR Expert Meeting / Conclusions of the Evaluation Meeting
	Section 1 Data requirements: ***3*** Open points: ***4***			Section 1 Data requirements: 0- Open points: 3
1.1	Notifier to submit details of the GC headspace method of analysis for the impurity 5. (see reporting table 1(1))	Impurity 5 is analysed by Method 2005-0013102-02; Kraemer, F.; Date 2002-10-18; BCS Report No, Mo-02-016109. The validation report is "Validation Report for Method 2005-0013102-02 VB1.4-[redacted]", Kraemer, F.; date 2002-11-05; BCS Report no. MO-02-017600. Both studies were submitted on March 9, 2005.	June 2005: Details of the GC headspace method of the analysis for the impurity 5 ([redacted]) are given. Method: see Kraemer, F.; MO-02-016109 Validation: see Kraemer F.; MO-02-017600	EPCO 30 (05. – 07.07.2005): Data requirement fulfilled
	Open point 1.1: RMS to amend the list of endpoints (list of representative uses) regarding the product name (code number). (see reporting table 1(5))		June 2005: List of endpoints has been amended. September 2006: List of endpoints has been amended. Open point considered closed.	EPCO 30 (05. – 07.07.2005): Open point still open Evaluation meeting (4-6.12.2006) The endpoints have been amended and the open point is closed.

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO and PRAPeR Expert Meeting / Conclusions of the Evaluation Meeting
1.2	Notifier to submit: 3. A 5 batch analysis of the large scale production; 4. For the compound which is analysed with GC-FID, a confirmatory method using specific detectors with the same method (e.g. GC-MS) or data to confirm the identity of the impurities revealed by chemical analysis must be provided to address the requirement of the Directive on the specificity of the method(s). (see reporting table 1(12))	The new 5 batch analysis of the large scale production is described in Rüngeler, W., 2004-09-15; BCS Report No. MO-04-009359 in connection with the corresponding analytical methods and validation reports. The 5 batch analysis also contains the confirmatory methods mentioned in the data requirement. A bridging statement explaining and justifying the new specification (P. Linke-Ritzer, L. Diesing, C. Maus, 2005-02-01, BCS Report No. MO-05-004882; including references) was also submitted. The MA study, the bridging statement, and all references were submitted on March 9, 2005.	June 2005: A 5-batch analysis of the large scale production has been submitted. Including the analytical methods and validation data of all (specified) impurities. The compound which is analysed with GC-FID in the 5-batch analysis of the pilot plant batches, is in the new 5-batch analysis analysed with HPLC, identity is confirmed by UV-spectrum comparison. The large scale production pathway is shortened as two intermediates are commercially available. Purity of the commercially available intermediates [redacted] and [redacted] are not submitted. A bridging statement explaining and justifying the new specification was also submitted. This should be evaluated by (eco)tox.	EPCO 30 (05. – 07.07.2005): Data requirement fulfilled. Data requirement 1.4 identified.
1.4	Notifier to provide purity of two new starting materials. This data requirement was indentified at the EPCO 30 meeting		September 2006: [redacted] See revised addendum to volume 4 (September 2006). Data requirement considered fulfilled.	EPCO 30 (05. – 07.07.2005): Data requirement identified. Evaluation meeting (4-6.12.2006) The data requirement is addressed the data is summarised in addendum to volume 4 dated September 2006.

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO and PRAPeR Expert Meeting / Conclusions of the Evaluation Meeting
	Message from EPCO 30 to experts of the sections ecotoxicology and mammalian toxicology: To confirm that new specification from full-scale production is acceptable.		September 2006: See sections mammalian toxicology and ecotoxicology. Point considered closed for FCE	Evaluation meeting (4-6.12.2006) This message has been conveyed to tox and ecotox and is closed for physchem.
	Note: Depending on the outcome of the residue expert meeting [see open point 3.3], it could be necessary to require further data with respect to an enforcement method for food of animal origin. (see reporting table 1(17))	A new method for enforcement of animal matrices (muscle, milk, liver, fat) for parent and BAJ 2740-enol was developed and is submitted together with the evaluation tables: Zimmer (2005), MO-05-005229 (ILV: Bacher (2005), MO-05-005724)	June 2005: For animal products spirodiclofen-enol is the residue of concern. An enforcement method to determine spirodiclofen-enol (M01) in cattle products (meat, milk, kidney, liver, fat) should be provided, since deuterated internal standards are not commonly available (Method 109720, see B.5.2.4 in the monograph) and implementation in an multiresidue method was not tested (Enforcement method 00086/M030 [extended revision of DFG Method S19], see B.5.2.1 in the monograph). A new method (Zimmer (2005) MO-05-005229) for enforcement of animal matrices (muscle, milk, liver, fat) for parent and BAJ 2740-enol and an ILV (Bacher (2005), MO-05-005724) are submitted. List of endpoints has been amended.	EPCO 30 (05. – 07.07.2005): Fulfilled

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO and PRAPeR Expert Meeting / Conclusions of the Evaluation Meeting
	Open point 1.2: Being aware that a data requirement is set for large scale batch analysis, this is not comprehensible from the list of endpoints. Therefore, it should be indicated that the minimum purity given in the list of endpoints is related to a pilot plant. (see reporting table 1(44))	The minimum purity of 95.5% which is currently given in the list of endpoints refers to a pilot plant production scale. According to the new MA-study (large scale production) the minimum purity is increased to 96.5%.	June 2005: The large-scale production leads to a technical product of higher purity than the pilot plant material. Therefore the certified limit of the active substance was increased from 955 g/kg to 965 g/kg. This has also been amended in the list of endpoints.	EPCO 30 (05. – 07.07.2005): Open point fulfilled

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO and PRAPeR Expert Meeting / Conclusions of the Evaluation Meeting
	Open point 1.3: RMS to confirm the residue definitions for monitoring for soil and water. Depending on the outcome of the expert meetings (fate and behaviour, ecotoxicology and toxicology) further data could be required. (see reporting table 1(45)) *continued* Open point 1.3: RMS to confirm the residue definitions for monitoring for soil and water. Depending on the outcome of the expert meetings (fate and behaviour, ecotoxicology and toxicology) further data could be required. (see reporting table 1(45))	The open point under 1(45) in the reporting table covers two different aspects: a) the question about the residue definition in soil and water and b) the question about the relevance of an impurity. c) residue definition in soil and water: The residue definition for <u>water</u> includes the parent compound and BAJ 2740-enol, which is a major hydrolysis product. Concerning a separate residue definition for ground water, see Open point 4(3). The residue definition for <u>soil</u> as given in the DAR should only include the parent compound and BAJ 2740-enol. All other metabolites are ecotoxicologically not relevant – See also BCS **position paper 1_3a** (Kaune, A., Maus, C., 2005; BCS Document no MO-05-006082). d) relevant impurities: In reporting table 1(45) EFSA additionally raises the question about the relevance of an impurity in the technical material. Please see Bayer CropScience **position paper 1_3b** (Linke-Ritzer, P., Nicolaus, B., 2005; BCS Document no MO-05-006689).	June 2005: The residue definition for <u>water</u> and <u>soil</u> includes the parent compound and BAJ 2740-enol. BAJ 2740-Enol is an impurity in technical spirodiclofen, which has to be categorised as significant because of its concentration in the technical active substance. However, due to its toxicological and ecotoxicological properties it is not a relevant impurity. <u>September 2006:</u> Outcome EPCO-26: groundwater res.def = parent surface water res.def = parent + enol Outcome EPCO 27: soil res.def = parent For water acceptable analytical methods for monitoring are available. For soil acceptable methods for monitoring the parent and for the -enol methods are available. No data requirements. Open point considered closed.	<u>EPCO 30 (05. – 07.07.2005):</u> Open point still open. <u>Evaluation meeting (4-6.12.2006)</u> The first point to be addressed was the residue definition for water and soil and this has been clarified. The second point was related to the impurity BAJ 2740-Enol and its relevance and this has been transferred to Tox and Ecotox and it is closed for physchem.

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO and PRAPeR Expert Meeting / Conclusions of the Evaluation Meeting
1.3	Notifier to submit solubility in water and partition co-efficient data at pH 7. (see reporting table 1(51))	The studies have been started; the reports are not finalised yet and will be submitted as soon as possible. The report numbers, the titles and the preliminary results are: Report No.: PA05/027 Title: Spirodiclofen, BAJ 2740 (AE 1344097) Water Solubility at pH 7 Result: Solubility in water at 20°C: cs = 0.19 mg / L = 190 µg / L Report No.: PA05/028 Title: Spirodiclofen, BAJ 2740 (AE 1344097) Partition Coefficient 1-Octanol / Water at pH 7 Result: log Pow = 5.1	June 2005: The notifier submitted studies of the water solubility and partition co-efficient of spirodiclofen at pH 7, which full-fill data requirement 1.3. List of endpoints has been amended.	EPCO 30 (05. – 07.07.2005): Data requirement fulfilled
	Open point 1.4: MS to discuss in an expert meeting as a general point whether it is acceptable to address both annex points on oxidising properties (for the active substance and the formulation) only with justifications based on a theoretical assessment. (see reporting table 1(53))		June 2005: According to expert meeting (EPCO 25), it is acceptable to address both annex points on oxidising properties (for the active substance and the formulation) only with justifications based on a theoretical assessment.	EPCO 30 (05. – 07.07.2005): Open point fulfilled

1.5	Data dap proposed at the evaluation meeting:		April 2009: a report with a storage stability study of Spirodiclofen 240 SC in HDPE (2 weeks, 54°C) was submitted and evaluated. The a.s. content and the content of the impurities N,N-dimethylacetamide (<0.05% before and after storage) and BAJ 2740-enol (<0.08% before and after storage) were unchanged. The package was found to be stable. Point considered addressed.	Evaluation Meeting (04.-06-12.2006): As the impurities 3-(2,4-dichlorophenyl)-4-hydroxy-1-oxaspiro[4.5]dec-3-en-2-one (BAJ-2740 enol) and N,N-dimethylacetamide are consider relevant storage stability data where the impurities are analysed forin the PPP before and after storage is missing. Data requirement open. PRAPeR 66 (21 – 24 April 2009): Data requirement closed
1.6	Data requirement proposed at the evaluation meeting:		April 2009: a report with a description of HPLC/UV method AM011108MF1 to determine spirodiclofen and the impurities BAJ-2740 enol and N,N-dimethylacetamide in the plant protection product and another one with validation for this method were submitted and evaluated. The submitted validation was acceptable for spirodiclofen and supported LOQs of 0.05% w/w for N,N-dimethylacetamide and 0.08% for BAJ-2740 enol. Whether the method of analysis for the byproducts is capable to determine each byproduct at the maximum level, cannot be established at present, since no maximum levels for both byproducts have been agreed yet (List of Endpoints of EFSA Scientific Report (2007) 104). List of Endpoints amended.	Evaluation Meeting (04.-06-12.2006): As the impurities 3-(2,4-dichlorophenyl)-4-hydroxy-1-oxaspiro[4.5]dec-3-en-2-one (BAJ-2740 enol) and N,N-dimethylacetamide are consider relevant validated methods of analysis for these compounds in the PPP are missing. Data requirement open. PRAPeR 66 (21 – 24 April 2009): Data requirement closed New open point: Method for relevant impurities to be transferred to Vol 3 New open Point EFSA: Check whether the methods are appropriate for the maximum levels of the impurities set following the Tox meeting.

	New open point 1.5 Method for relevant impurities to be transferred to Vol 3			PRAPeR 66 (21 – 24 April 2009): Open point open
	New open Point 1.6: EFSA:to check whether the methods are appropriate for the maximum levels of the impurities set following the Tox meeting.			PRAPeR 66 (21 – 24 April 2009): Open point open
1.7	Data requirement proposed at the evaluation meeting:		April 2009: reports with spectra (IR-,1H-NMR, 13C-NMR, MS- and UV–spectra of the impurities N,N-dimethylamine and BAJ 2740-enol were submitted, evaluated and found to be acceptable. Point considered addressed.	Evaluation Meeting (04.-06-12.2006): As the impurities 3-(2,4-dichlorophenyl)-4-hydroxy-1-oxaspiro[4.5]dec-3-en-2-one (BAJ-2740 enol) and N,N-dimethylacetamide are consider relevant spectra are missing. Data requirement open. PRAPeR 66 (21 – 24 April 2009): Data requirement closed
	New open point 1.7: RMS to amend the list of end points according to the discussions during thef PRAPeR 66 meeting.			PRAPeR 66 (21 – 24 April 2009): Open point open

REPORT OF PRAPeR EXPERT MEETING 68

SPIRODICLOFEN

Rapporteur Member State: NL

Specific comments on the active substance in the section

5. Ecotoxicology

are already listed in the relevant reporting table. Comments submitted for this meeting are listed below.

1. Comments submitted for this meeting:

Date	Supplier	File Name
none		

2. Documents submitted for meeting:

Date	Supplier	File Name
April 2009	NL	spirodiclofen_addendum_B9_April 2009.doc
April 2009	NL	spirodiclofen_essential studies_September 2006_revised April 2009.doc
April 2009	NL	spirodiclofen_evaluation table rev 3-0_revised April 2009
April 2009	NL	spirodiclofen_list of endpoints_revised April 2009.doc
04-03-2005	NL	Spirodiclofen_reporting_table_rev1-1_(04-03-2005).doc

3. Documents tabled at the meeting:

Date	Supplier	File Name
none		

The conclusions of the meeting were as follows:

4. Data on preparations: Envidor SC 240

5. Classification and labelling: not discussed

10. Recommended restrictions/conditions for use: none

11. Reference list: not discussed

Areas of concern: none

Appendix 1: Discussion table: SPIRODICLOFEN

Appendix 2: Evaluation table

Appendix 1: Discussion Table, Spirodiclofen (In)

	Subject	Discussion Expert Meeting	Conclusions Expert Meeting
	Message from EPCO 30 to experts of the sections ecotoxicology and mammalian toxicology: To confirm that new specification from full-scale production is acceptable <u>Evaluation meeting (4-6.12.2006)</u> The new specification is considered as acceptable with regard to mammals and aquatic organisms. The information is insufficient to conclude on soil dwelling organisms. Data requirement Applicant to submit the studies on the aquatic organisms and soil organisms confirming the equivalence of technical material and the ecotoxicological non-relevance of the 3 new impurities.	The substance was discussed already years ago. The only point for discussion now has to do with the changes in the specification. New impurities are present in the new specification. In the addendum, these are discussed and it is concluded that the new impurities are not of ecotoxicological relevance. The new technical material was tested on soil organisms and the toxicity was not increased compared to the old technical material. No comments. Data requirement closed.	Data requirement closed.

	Subject	Discussion Expert Meeting	Conclusions Expert Meeting
	This data requirement is regarded as a technical data requirement since the RMS already received the studies with aquatic organisms and the studies with soil organisms are expected to be submitted in March 2007.		
	Transferred from section 1, open point 1.3: To address the ecotoxicological relevance of the impurity BAJ 2740-Enol. <u>Evaluation meeting (4-6.12.2006)</u> BAJ 2740-enol is also a metabolite in the environment. The risk to the environment was assessed as low. Therefore BAJ 2740-enol is not considered to be an ecotoxicologically relevant impurity.		

Appendix 2: Evaluation table

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the evaluation group
	Section 5 Data requirements: ***3*** Open points: ***9***			Section 5 Data requirements:0**-** Open points: ***0***
	Open point 5.1: RMS to prepare an addendum to clarify if further data is needed to address the risk to aquatic organisms or not. (see reporting table 5(3))	The use pattern of spirodiclofen with a single seasonal application as well as the very fast dissipation from surface water (<2 d) indicates that chronic exposure of aquatic organisms is unlikely. However, the toxicity observed under chronic exposure conditions has been taken into consideration and a full risk assessment has been provided by the notifier, including risk mitigation options.	May 2005: The toxicity observed under chronic exposure conditions has been taken into consideration and a full risk assessment has been provided in the addendum of May 2005. Open point fulfilled.	EPCO 27 (06.– 10.06.2005): Open point 5.1 fulfilled. New open points 5.10 and 5.11 proposed.
	New open point 5.10. RMS to establish how the sensitive life stage of fish was determined for the ELS test. This open point was proposed at the EPCO 27 meeting.		September 2006: At first a range-finder ELS-pulse-experiment was conducted as limit-test at the concentration of 40 ug a.s./L (practical limit of water solubility of BAJ 2740) to determine the most sensitive early life stage of rainbow trout with regard to growth effects after a limited duration (10 days) of exposure. Eight groups (A-H; 2 replicates per group, each with 35 eggs/15 alevins) at different early life stages (from freshly fertilized eggs up to the juvenile fry after swim-up) between study day 0 and study day 80 were	EPCO 27 (06.– 10.06.2005): Open point still open. Evaluation meeting (4-6.12.2006) Open point fulfilled

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the evaluation group
			consecutively exposed to a 10-day-pulse of BAJ 2740 under flow-through conditions. The range-finder was terminated after a total duration of 97 days. The early life stage which was pulsed between study day 60-70 (PHD 25-35) was indicated to be the most sensitive early life stage based on growth effects, expressed as dry weight and standard length. In a second range-finder test a dose-response pulse-experiment with the most sensitive early life stage of rainbow trout (juvenile fry/PHD 25-35) was conducted to show whether the initial sensitivity to BAJ 2740 (NOEC = 1.95 ug a.s./L) is still given with a limited exposure time of only 10 days. Five test levels each with 30 fish (PHD 26 at test beginning) were continuously exposed for 10 days of the 36 day test at 2.50, 5.00, 10.0, 20.0 and 40.0 ug a.s./L under flow-through conditions. After 10 days the entire test system was converted to clean water. The test was terminated after a total duration of 36 days (fish were in total 96 days old) and the overall NOEC (based on standard length) was < 2.50 ug a.s./L. Thus the results of the regular ELS-study were confirmed even though fish were shorter exposed.	

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the evaluation group
			Open point considered closed.	
	New open point 5.11: RMS to amend list of endpoints (TERs to be recalculated comparing NOECs for fish and *Daphnia* with initial PECs) This open point was proposed at the EPCO 27 meeting.		September 2006: The list of endpoints has been amended by comparing the NOEC-values for fish and *Daphnia* with initial PEC-values. Open point considered closed.	EPCO 27 (06.– 10.06.2005): Open point still open. Evaluation meeting (4-6.12.2006) Open point fulfilled
	Open point 5.2: RMS to amend the list of endpoints regarding the BCF (add or adjust based on total radio-activity). (see reporting table 5(6))		May 2005: The list of endpoints has been amended regarding the BCF. Open point fulfilled.	EPCO 27 (06.– 10.06.2005): Open point 5.2 fulfilled.
	Open point 5.3: RMS to prepare an addendum with a revised risk assessment for birds and mammals according to the final version of the Guidance Document on Birds and Mammals to be discussed in an expert meeting. (see reporting table 5(7))	A risk assessment to birds and mammals according to the final version of the Guidance Document on Birds and Mammals for review by the RMS has been provided by the notifier. See BCS **position paper 5_3** (Nicolaus, B., 2005; BCS Document no MO-05-006379) and Bowers (2001), MO-03-005295.	May 2005: Revised risk assessment for birds and mammals according to the final version of the Guidance Document on Birds and Mammals has been made. See addendum of May 2005. Open point fulfilled.	EPCO 27 (06.– 10.06.2005): Open point 5.3 fulfilled. New open point 5.12 proposed.

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the evaluation group
	New open point 5.12: RMS to amend list of endpoint with respect to the Mammalian repro LOEC of 350 mg a.s./kg diet (26.2 mg a.s./kg bw). This open point was proposed at the EPCO 27 meeting.		September 2006: The list of endpoints has been amended on this point. Open point considered closed.	EPCO 27 (06.– 10.06.2005): Open point still open. Evaluation meeting (4-6.12.2006) Open point fulfilled
	Open point 5.4: RMS to prepare an addendum with a revised risk assessment regarding bioaccumulation using the BCF-value based on total radioactivity (BCF of 491 L/kg). (see reporting table 5(9))	For the risk assessment on birds and mammals with respect to secondary poisoning and food chain accumulation the notifier considers the BCF for spirodiclofen itself as the most appropriate value to assess the risk posed by the parent compound. Following the OECD testing guideline 305 the BCF_{fish} should be based upon the parent compound in fish despite total radioactive residues are additionally determined. To address the risk of secondary poisoning caused by **metabolites** of spirodiclofen, a BCF of 491 may be taken into account.	May 2005: Revised risk assessment regarding bioaccumulation using the BCF-value on total radioactivity (BCF of 491 L/kg) has been made. See addendum of May 2005. Open point fulfilled.	EPCO 27 (06.– 10.06.2005): Open point 5.4 fulfilled.
	Open point 5.5: MS to discuss the setting of the NOEC for mammals in an expert meeting. (see reporting table 5(12)) *continued*	BCS supports the argumentation by the RMS (reporting tables 5(22)) that the ecotoxicologically relevant endpoint is 350 ppm.	May 2005: The comment of SLO was: *"Refinement of the NOEC based on the assumption that continuous exposure does not occur is not acceptable. The decline in residue is accounted for at the exposure side and should not be refined on the toxicity*	EPCO 27 (06.– 10.06.2005): Open point 5.5 fulfilled.

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	Open point 5.5: MS to discuss the setting of the NOEC for mammals in an expert meeting. (see reporting table 5(12))		*side."* The decline in residue is indeed accounted for at the exposure side, but only for a limited period (21 days). In the study there is a continuous exposure to constant levels of spirodiclofen for 16 weeks. Under a practical scenario involving a seasonal treatment only, continuous exposure for such a long time is very unlikely due to decline of residues.	
	Open point 5.6: RMS to transfer information (avian toxicity) from column 3 of the reporting table to an addendum to be discussed in an expert meeting. (see reporting table 5(19))	An avian reproduction study conducted with Mallard Duck is available, confirming the results on the first species (Bobwhite quail). No effects on reproduction up to the highest tested dose were observed, the no effect level was calculated to be 111 mg/kg b.w./day. (Bowers (2001), MO-03-005295; see attachment).	May 2005: The information from column 3 of the reporting table has been transferred to an addendum. See addendum of May 2005. Open point fulfilled.	EPCO 27 (06.– 10.06.2005): Open point 5.6 fulfilled.
5.1	Notifier to address the effects on bee brood (e.g. a field study, labelling). (see reporting table 5(24))	The notifier has proposed an appropriate labelling in order to minimize the risk to bee brood. The comment of the Rapporteur to address, in addition to the restriction on application during flowering crops, also flowering weeds, is accepted by the notifier.	May 2005: To address the risk to bee brood the notifier has proposed an appropriate labelling in order to minimize the risk to bee brood, e.g. no use of the product during flowering of the crop and avoiding that there are flowering weeds present (e.g. by mowing the weeds). See also addendum of May 2005. Data requirement fulfilled.	EPCO 27 (06.– 10.06.2005): Data requirement fulfilled (provided labelling is practical)
	Open point 5.7:		May 2005:	EPCO 27 (06.– 10.06.2005):

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	RMS to transfer information regarding risk to other non-target arthropods from column 3 of the reporting table to an addendum to be discussed in an expert meeting. (see reporting table 5(25))		The information from column 3 of the reporting table has been transferred to an addendum. See addendum of May 2005. Open point fulfilled.	Open point fulfilled.
	Open point 5.8: MS to discuss the risk to NTA in an expert meeting. (see reporting table 5(26))	Spirodiclofen has a unique, novel Mode of Action which is clearly different to that of IGRs (spirodiclofen inhibits lipid biosynthesis but has no effects on chitin biosynthesis). Furthermore the symptoms of poisoning as well as the biological spectrum for spirodiclofen are different to IGRs. Consequently it is also classified differently to IGRs (MoA group 23 vs 15 for IGRs) by IRAC. Therefore the comparison with IGRs is not justified.	May 2005: RMS can agree with the statement provided by the notifier. But even when the compound is considered as an IGR the data requirements have been fulfilled. According to the Escort 2 guidance document testing of IGRs should be conducted with *T. pyri* and one other species (e.g. *Coccinella septempunctata, Orius laevigatus* or *Chrysoperla carnea*). For spirodiclofen testing was done with *T. pyri* and *Chrysoperla carnea*. In these tests not only mortality but also reproduction was evaluated. So, according to the available guidance the appropriate tests are available. Maybe other tests must be developed in which insects are tested by taking up food. See also addendum of May 2005.	EPCO 27 (06.– 10.06.2005): Open point fulfilled.
5.2	Notifier to submit the new chronic study with fish.	A higher tier study on the chronic toxicity of spirodiclofen to fish was	May 2005: Notifier has submitted the new chronic	EPCO 27 (06.– 10.06.2005): Data requirement fulfilled.

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	(see reporting table 5(35))	conducted simulating exposure conditions that are more realistic to potential entrance into surface water and its behaviour therein (BCS Document No: MO-02-014087, Dorgerloh, M, & Sommer, H., Chronic effects of BAJ 2740 on selected early life stages of rainbow trout (Oncorhynchus mykiss) under more realistic conditions of exposure) The study has been submitted by BCS on March 9, 2005. A revised assessment of the chronic risk to aquatic organisms is presented in BCS **position paper 5_9** (Nicolaus, B., 2005a; BCS Document no MO-05-006867).	study with fish. This study has been evaluated by the RMS. The NOEC is 0.020 mg/L. The results of the study are used for risk assessment. The revised risk assessment is presented in the addendum of May 2005. Data requirement fulfilled.	
	Open point 5.9: MS to discuss the chronic risk to aquatic organisms in an expert meeting. (see reporting table 5(35))	A revised assessment of the chronic risk to aquatic organisms is presented in BCS **position paper 5_9** (Nicolaus, B., 2005a; BCS Document no MO-05-006867).	May 2005: A revised chronic risk assessment for aquatic organisms is presented in the addendum of May 2005. Open point fulfilled.	EPCO 27 (06.– 10.06.2005): Open point fulfilled.
5.3	Notifier to submit summary on endocrine effect on fish to the RMS. (see reporting table 5(41))	Statement has been submitted by BCS on March 9, 2005.	May 2005: The notifier has submitted a statement regarding the endocrine effect on fish. This is presented in the addendum of May 2005. Data requirement fulfilled.	EPCO 27 (06.– 10.06.2005): Data requirement fulfilled. New open point 5.13 proposed.
	New open point 5.13: RMS to consider German		September 2006: The German national assessment of	EPCO 27 (06.– 10.06.2005): Open point still open.

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	national assessment of the ELS study using the enol metabolite. This open point was proposed at the EPCO 27 meeting.		the ELS study using the enol metabolite has been considered. The conclusion of the German assessment is that the study can be accepted. In place of a NOEC-value of 190 µg/L, Germany has the opinion that an EC10-value of 21.3 µg/L for effects on the sex ratio of the enol-metabolite must be taken for assessment. NL agree with this endpoint. The EC10-value of 21.3 µg/L is higher than the long-term endpoint for the parent (20 µg/L) and the exposure of the metabolite will be lower than the exposure value of the parent. Therefore, the risk of the enol-metabolite is sufficiently covered by the parent. The endpoint list is amended on this point. Open point considered closed.	Evaluation meeting (4-6.12.2006) Open point fulfilled.
	Message from EPCO 30 to experts of the sections ecotoxicology and mammalian toxicology: To confirm that new specification from full-scale production is acceptable		September 2006: The large-scale production leads to a technical product of higher purity than the pilot plant material. As a consequence the limits of some impurities could be considerably decreased ([redacted] from [redacted] g/kg to [redacted] g/kg and [redacted] from [redacted] g/kg to [redacted] g/kg). All other impurities identified in the material from the pilot plant production	Evaluation meeting (4-6.12.2006) The new specification is considered as acceptable with regard to mammals and aquatic organisms. The information is insufficient to conclude on soil dwelling organisms. Data requirement Applicant to submit the studies on the aquatic organisms and soil organisms confirming the equivalence of technical

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			process occur in about the same amount in the samples from the large-scale production. Therefore their certified limits remain unchanged. Three additional impurities were identified in the new batches which were not detected in the pilot plant batches: [redacted], N,N-dimethylacetamide and [redacted] Their limits were set between ma. [redacted]g/kg and [redacted] g/kg. The notifier has sent the following ecotoxicological assessment with regard to the new impurities: *The impurity and byproduct profile of the current composition statement of the technical material differs from the profile of the former composition statement. Three new impurities or byproducts are specified:* [redacted] *(impurity # 05),* ***N,N-Dimethylacetamide*** *(impurity # 06), and* [redacted] *(impurity # 07). For two of them basic ecotoxicological data are available, for the third one, they can be extrapolated from a* [redacted] *On* [redacted] *(impurity # 05), no ecotoxicological data are available. However, this impurity is structurally very similar to* [redacted]*, which is an* [redacted] *in*	material and the ecotoxicological non-relevance of the 3 new impurities. This data requirement is regarded as a technical data requirement since the RMS already received the studies with aquatic organisms and the studies with soil organisms are expected to be submitted in March 2007. PRAPeR 68 (4 – 8 May 2009): Data requirement closed.

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			the [redacted] (for chemical structure see page 5 above). The [redacted] was examined for its effects to fish and Daphnia. The LC_{50}/EC_{50} figures found were ≥ 0.4 mg/L (fish), and ≥ 0.77 mg/L (Daphnia), respectively. Due to the structural similarity of both substances, it can be assumed that the intrinsic toxicity is comparable. Therefore the values of [redacted] were taken for the risk assessment of [redacted]. When the maximum concentration of the impurity in the technical material ([redacted] g/kg = [redacted] kg/kg) is compared to the toxicity values for [redacted] to fish and Daphnias, the resulting toxicity figures are equal to or even in excess of the EU trigger value of 100 mg/L ([redacted] mg/L : [redacted] = 100 mg/L; [redacted] mg : [redacted] = 192.5 mg/L). *Furthermore [redacted] is less soluble in water and more lipophilic than [redacted] Therefore, uptake in animal and plant tissues and thereby also toxicity to aquatic organisms is expected to be greater in [redacted]. With respect to bioavailability the impurity [redacted] has a decreased ecotoxicity potential. Therefore the new certified limit of [redacted] in*	

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			technical spirodiclofen is of no ecotoxicological significance. ***N,N - Dimethylacetamide*** *(impurity # 06) is of low toxicity to fish, Daphnia and algae, with LC_{50} values above 500 mg/l (data from the material safety data sheet). This compound is therefore not classified (LC_{50} > 100 mg/L) for ecotoxicological properties under EU classification criteria. The new certified limit of N,N - Dimethylacetamide in technical spirodiclofen is of no ecotoxicological significance.* [redacted] *(impurity # 07) is not toxic neither to fish nor to Daphnia following data from the material safety data sheet (Daphnia: LC_{50} (estimated) > 100 mg/L; for algae (estimated) EC_{50} between 10 and 100 mg/L).* *The new technical Spirodiclofen has a specified limit of max. [redacted] g/kg [redacted]. When the toxicity value for [redacted] to algae is compared to the new certified limit, the resulting toxicity figure is in excess of the EU trigger value of 100 mg/L ([redacted] mg/L : [redacted] = 2000 mg/L). The level of [redacted] in technical Spirodiclofen is therefore not*	

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			of ecotoxicological significance. **Reaction RMS:** The conclusion of the notifier is that all three new impurities are not of ecotoxicological significance. But this conclusion is only based on data for aquatic organisms. To the opinion of the RMS more ecotoxicological data should be available to prove the ecotoxicological insignificance of the impurities. At least data on several soil organisms, e.g. earthworms and soil micro-organisms, are necessary. Further the underlying studies of the aquatic toxicity results, presented above, are not available. These studies should be submitted by the notifier. Hence, at this moment no conclusion regarding the ecotoxicological significance of the three new impurities can be drawn. April 2009 The notifier has submitted the underlying studies of the aquatic toxicity results and the toxicity studies on earthworms and soil micro-organisms. These studies are summarised and evaluated in the addendum of April 2009. The overall conclusion is that based on	

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			the submitted studies on the toxicity of the active substance (together with the new impurities) and the new impurities itself for aquatic organisms and soil organisms it can be concluded that the new impurities are not of ecotoxicological significance.	
	Transferred from section 1, open point 1.3: To address the ecotoxicological relevance of the impurity BAJ 2740-Enol.			Evaluation meeting (4-6.12.2006) BAJ 2740-enol is also a metabolite in the environment. The risk to the environment was assessed as low. Therefore BAJ 2740-enol is not considered to be an ecotoxicologically relevant impurity. Open point closed

Report of PRAPeR Expert MEETING 69

SPIRODICLOFEN

Rapporteur Member State: NL

Specific comments on the active substance in the section

2. Mammalian Toxicology

are already listed in the relevant reporting table. Comments submitted for this meeting are listed below.

1. Comments submitted for this meeting:

Date	Supplier	File Name
27.04.2009	DE	Comments of Germany on the Addendum (April 2009) on Spirodiclofen

2. Documents submitted for meeting:

Date	Supplier	File Name
Nov. 2006	NL	Spirodiclofen final addendum (Nov 2006).doc
April 2009	NL	spirodiclofen_addendum_B6_April 2009.doc
April 2009	NL	spirodiclofen_essential studies_September 2006_revised April 2009.doc
April 2009	NL	spirodiclofen_evaluation table rev 3-0_revised April 2009
April 2009	NL	spirodiclofen_list of endpoints_revised April 2009.doc
04-03-2005	NL	Spirodiclofen_reporting_table_rev1-1_(04-03-2005).doc
2009-04-27	NL	Sprirodiclofen_Addendum_German Comments_2009-04-27.doc

3. Documents tabled at the meeting:

Date	Supplier	File Name
none		

The conclusions of the meeting were as follows:

4. **Data on preparations:** Envidor SC 240

5. **Classification and labelling:** not discussed

6. **Recommended restrictions/conditions for use:** none

7. **Reference List:** not discussed

Areas of concern: none

Appendix 1: Discussion table: SPIRODICLOFEN

Appendix 2: Evaluation table

Appendix 1: Discussion Table, Spirodiclofen (In)

2. Mammalian toxicology

No.	Subject	Discussion Expert Meeting	Conclusions Expert Meeting
	Added by RMS, as it was only mentioned in the discussion table, and not copied to evaluation table: Metabolites M01-M16 are toxicologically relevant. The RMS is to clarify whether BAJ 2740- dihydroxy and BAJ 2740-ketohydroxy are rat metabolites. <u>Evaluation meeting (4-6.12.2006)</u> BAJ2740-ketohydroxy and BAJ2740-dihydroxy are not rat metabolites.		
	Transferred from section 1, open point 1.3: To address the toxicological relevance of the impurity BAJ 2740-Enol. <u>Evaluation meeting (4-6.12.2006)</u> As spirodiclofen is proposed		

No.	Subject	Discussion Expert Meeting	Conclusions Expert Meeting
	for classification as R40, all rat metabolites of spirodiclofen (e.g. BAJ 2740-enol) are considered toxicologically relevant.		
	New open point 2.16 (added by RMS): Evaluation of the full scale specification.	RMS presented an Addendum to the DAR with new full scale production of spirodiclofen. There were three new impurities: [redacted] – acute oral toxicity (LD50>2500 mg) and Ames test (negative) N,N-dimethylacetamide – Repro2, R61, Harmful, R20/21. A threshold value has been set in USA and Germany as 10 ppm (36 mg/m^3). The RMS concludes that a specified limit of max. [redacted] g/kg can be supported from a toxicological perspective. This impurity has not been tested in the technical specification. The lowest substance specific trigger value for classifcation (Repro2) is 5% concentration. [redacted] is a main [redacted] following [redacted] of [redacted]. Thus, this compound can be regarded as covered by the toxicological studies performed with the parent molecule and the specified limit of max. [redacted] g/kg is toxicologically acceptable. Experts considered that the new specification from full scale prodcution is acceptable. Open point fufilled	Open point fulfilled Experts considered that the new specification form full scale production is acceptable
	New open point 2.17 (added by RMS): Evaluation of the developmental neurotoxicity (DNT) study and the supplementary DNT study.	The DNT rat studies in the Addenda to the DAR dated November 06 and April 2009 were presented by the RMS. In the first study there was increased incidence of deceased memory performance at all dose levels in females. There was no dose response relationship. In the second	Open point fulfilled. The experts concluded that there were no developmental nerotoxicology effects and the NOAEL can be set as 1500 ppm

No.	Subject	Discussion Expert Meeting	Conclusions Expert Meeting
		study no significant differences between control and treated groups was demonstrated at any dose level. Therefore the experts concluded that there were no developmental nerotoxicology effects and the NOAEL can be set as 1500 ppm (119 mg/kg bw/d). Open point fulfilled.	(119 mg/kg bw/d).
	New open point 2.18 (added by RMS): The dermal absorption values and the revised risk assessment to be confirmed at the expert meeting.	Based on the results from the monkey study dermal absorption vales of 10% for the concentrate and 65% for the dilution were agreed previously. However, based on these values there were no safe uses. A further study in monkey and an in vitro study with rat and human skin all performed with the representative formulation were submitted and presented in the Addendum to the DAR. The monkey study was disregarded as it was performed on 1 monkey (and there are ethical issues) and therefore only the in vitro study was used to make the dermal absorption proposals of the RMS (0.4% for the concentrate and 3% for the dilution – these were taken from the human skin values). Experts agreed to the proposal of the RMS. Open point fulfilled.	Open point fulfilled. Experts agreed to the proposal of the RMS.

Appendix 2: Evaluation table

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
	Section 2 Data requirements: ***1*** Open points: ***14***			Section 2 Data requirements: 0**-** Open points: 0**-**
	Open point 2.1: The oral absorption value to be confirmed at an expert meeting. (see reporting table 2(1)) *continued*	The RMS used a correction factor of 0.58 to reflect an allegedly incomplete absorption of spirodiclofen from the gastro-intestinal tract. This value obviously originates from a single dose study (3 mg/kg bw) where renal excretion was ca. 58 % in male rats and 75 % in females. A correction factor of 0.58 is regarded to be over-conservative as it does not include spirodiclofen excreted via bile. In a bile cannulation experiment ca. 12 % of the radioactivity was identified in the bile fluid. This finding and the fact that in a repeated dose study > 70 % of the radioactivity were excreted in the urine of males and females, support an overall correction factor of 0.7.	June 2005: The use of 0.58 for oral absorption is considered worst-case for risk assessment purposes. The value of 0.58 was based on excretion of radiolabel in urine 24 hours after administration of 2 mg/kg bw. However, a longer collection period should have been considered. Within the available studies, data could have been derived after 48 hours, which would have resulted in oral absorption of 0.64 for males and 0.76 for females. These latter data are now included in the endpoint list. For risk assessment purposes, the difference between 0.58 and 0.64 is considered negligible. A systemic AOEL of 0.009 mg/kg bw/day (0.63 mg/day) is calculated instead of an AOEL of 0.008 mg/kg bw/day (0.56 mg/day), and no new occupational risk assessment was performed. The AOEL however, is adapted in the critical endpoint list and addendum Furthermore, indeed data on bile	EPCO 28 (27.06. – 01.07.2005): A value of 65% was considered appropriate on the basis of radioactivity in urine and tissues in males. Open point closed.

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
	Open point 2.1: The oral absorption value to be confirmed at an expert meeting. (see reporting table 2(1))		cannulation rats were available. However, in this study the urinary excretion was quite low: following administration of 1 mg 14C-spirodiclofen/kg bw to bile duct cannulated male rats 62.8 % of recovered radioactivity was excreted within 24 h, i.e. 22.8% in urine, 28.7 % in faeces and 11.3 % in bile.	
	Open point 2.2: The endocrine disrupting properties of the compound to be discussed at an expert meeting. (see reporting table 2(4))	An independent scientific evaluation by OpdenKamp, title “The possible endocrine effects of BAJ 2740. A critical evaluation” is available as BCS **position paper 2_2** (van Sittert, N. J., Krüse, J., Groeneveld, C. N., 2002; BCS Document no MO-02-011326).	June 2005: See addendum.	EPCO 28 (27.06. – 01.07.2005): Spirodiclofen is considered an endocrine disruptor in that it interferes with steroid hormone synthesis. NOAELs were determined in reproduction and chronic studies, together with the mechanistic investigations indicated no additional safety factors were appropriate. Open point closed.
	Open point 2.3: RMS to present data (evaluated tissue of toxicokinetic studies) in an addendum. To be discussed together with open point 2.1 at an expert meeting. (see reporting table 2(5)) *continued* Open point 2.3:	Apart from liver, kidney, plasma, gastro-intestinal tract and skin, the following tissues were analysed: erythrocytes, spleen, renal fat, adrenal gland, testes, muscle, bone femur, hear, lung, brain, thyroid gland and carcass (Appendices 18-20, including the footnotes, p. 182-188 of Andersch, I. and Koester, J. (2000a), BCS Report no. MO-00-015111). In total bone femur (including the bone marrow) of male and female rats (single and repeated oral administration), no radioactivity was	June 2005: See addendum. Data on all studied tissues is now explicitly mentioned in the text.	EPCO 28 (27.06. – 01.07.2005): Data presented in Addendum Open point closed (see open point 2.1).

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
	RMS to present data (evaluated tissue of toxicokinetic studies) in an addendum. To be discussed together with open point 2.1 at an expert meeting. (see reporting table 2(5))	detected (p. 183, 185 and 187 of Andersch, I. and Koester, J. (2000a), BCS Report no. MO-00-015111). Radioactivity in testes was 0.003 and 0.0008 µg/g and thus below the limit of quantification (p. 34 of Andersch, I. and Koester, J. (2000a), BCS Report no. MO-00-015111)). Also, no radioactivity was detected in uterus and ovary of female rats and in the adrenal gland and thyroid gland of both male and female rats (p. 182-188 of Andersch, I. and Koester, J. (2000a), BCS Report no. MO-00-015111)).		
	Open point 2.4: MS to confirm the relevant NOAEL for the short-term studies at an expert meeting. (see reporting table 2(9))	See separate BCS **position paper 2_4** (Diesing, L., 2005)	June 2005: See addendum. Several details were included in the study summaries, and the NOAEL in the 14-w oral study in rats is increased to 8.1 mg/kg bw/d, after evaluation of newly submitted historical data on adrenal vacuolation in males. The lowest NOAEL (1.45 mg/kg bw/d) is found in the 1-year oral toxicity study in dogs.	EPCO 28 (27.06. – 01.07.2005): The RMS increased the NOAEL for the 14 week rat study to 100 ppm (8.1 mg/kg bw) based on adrenal cortical vacuolisation in females. The NOAEL was increased as a result of the historical control data provided by the notifier, which demonstrated that the vacuolisation observed in males at the next highest dose level was within the historical control range. The lowest overall short term NOAEL was considered to be that of 1.45 mg/kg bw (50 ppm) from the 1 year dog study and appropriate for the derivation of the AOEL. Open point closed.
	Open point 2.5:	BCS fully supports the RMS response	June 2005:	EPCO 28 (27.06. – 01.07.2005):

No.	Column A Conclusions of the EFSA Evaluation Meeting	Column B Comments from the main data submitter / applicant on the EFSA Evaluation Meeting conclusion	Column C Rapporteur Member State comments on main data submitter / applicant comments	Column D Recommendations EPCO Expert Meeting / Conclusions of the Evaluation Meeting
	The genotoxicity to be discussed at an expert meeting. (see reporting table 2(10))	and argumentation in reporting table 2(10). All available studies demonstrate that spirodiclofen has no genotoxic potential.	No comments, besides our comments in the reporting table 2 (10): An increased mutation frequency with and without metabolic activation was only observed in one culture and was not confirmed in the parallel treated culture nor in the second trial. Therefore, the observed increase was not considered toxicologically relevant. The performance of a second in vivo genotoxicity study is not considered necessary.	The meeting agreed with the opinion of the RMS that spirodiclofen had no genotoxic potential and that a further in vivo study was not necessary. Open point closed.
	Open point 2.6: MS to confirm the relevant NOAEL for the long-term studies at an expert meeting. (see reporting table 2(11))	See separate BCS **position paper 2_6** (Diesing, L., 2005a)	June 2005: See addendum. Several details were included in the study summaries, and the position paper was evaluated. However, the RMS is of the opinion that the NOAELs do not have to be adapted.	EPCO 28 (27.06. – 01.07.2005): The experts concluded that the relevant NOAEL for the long-term exposures (ADI) was confirmed as 1.45 mg/kg bw derived from the 1 year dog study. It was noted that a similar value for reference doses would be derived using the LOAEL of 4.1 mg/kg bw/day from the mouse study, which would require the use of an additional safety factor for extrapolation from a LOAEL to a NOAEL. The NOAEL in the 2 year rat is 6 mg/kg bw/day. Open point closed.
	Open point 2.7: MS to confirm the relevant NOAEL for the reproduction toxicity studies at an expert meeting.	See separate BCS **position paper 2_7** (Diesing, L., 2005b)	June 2005: See addendum. Several details were included in the study summaries, and the position paper was evaluated.	EPCO 28 (27.06. – 01.07.2005): The experts concluded that the proposed NOAEL for the reproduction toxicity studies was appropriate. It was noted that no NOAEL for parental effects was

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	(see reporting table 2(12))		However, the RMS is of the opinion that the NOAELs do not have to be adapted.	derived. However, effects noted were consistent with those seen in general toxicity studies. Open point closed.
	Open point 2.8: The carcinogenic effects to be discussed at an expert meeting. (see reporting table 2(13))	BCS fully supports the RMS response and argumentation in reporting table 2(13). See also separate BCS **position paper 2_2** (van Sittert, N. J., Krüse, J., Groeneveld, C. N., 2002; BCS Document no MO-02-011326).	June 2005: No comments in addition to reporting table (2(12)): From the mechanistic studies it was concluded that the carcinogenic potential by BAJ 2510 should be regarded as a non-genotoxic carcinogenic mechanism, since based on the mechanistic studies, BAJ 2510 interferes with steroid hormone synthesis at the level of general biochemical pathways. See also addendum.	EPCO 28 (27.06. – 01.07.2005): Carcinogenic effects were confirmed at high dose levels, but clear NOAELs were demonstrated. Classification with R40 was supported. Open point closed.
	Open point 2.9: MS to confirm the ADI at an expert meeting. (see reporting table 2(14)) *continued* Open point 2.9: MS to confirm the ADI at an expert meeting. (see reporting table 2(14))	Based on the argumentation provided for open points 2(6) and 2(7), BCS supports an ADI value of 0.015 mg/kg bw/day.	June 2005: No comments in addition to in reporting table (2(14)). It was concluded that spirodiclofen is non-genotoxic, and a non-genotoxic carcinogenic mechanism was proposed based on the mechanistic studies. Therefore, it is considered suitable to establish an ADI. The lowest overall NOAEL for non-neoplastic lesions of 1.45 mg/kg bw/day from a 52 week oral toxicity study in dogs, was supported by short-term toxicity studies with rat and dog, 18 months oral toxicity study with mice	EPCO 28 (27.06. – 01.07.2005): The ADI of 0.015 mg/kg bw confirmed by experts based on the 1 year dog study with a 100 fold factor. Open point closed.

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			and a 2-generation rat toxicity study with LOAELs ranging from 2.9 to 8.0 mg/kg bw/day. Furthermore, these LOAELs were based on critical effects comparable to those observed in the 52 week oral toxicity study with dogs. As there seems to be no effect of exposure duration, it was considered suitable to use the clear NOAEL of 1.45 mg/kg bw/day for the establishment of the ADI. See also addendum. ADI is set at 0.015 mg/kg bw/d	
	Open point 2.10: MS to confirm the AOEL at an expert meeting. (see reporting table 2(15))	The RMS used a correction factor of 0.58 to reflect an allegedly incomplete absorption of spirodiclofen from the gastro-intestinal tract. This value obviously originates from a single dose study (3 mg/kg bw) where renal excretion was ca. 58 % in male rats and 75 % in females. A correction factor of 0.58 is regarded to be over-conservative as it does not include spirodiclofen excreted via bile. In a bile cannulation experiment ca. 12 % of the radioactivity was identified in the bile fluid. This finding and the fact that in a repeated dose study > 70 % of the radioactivity were excreted in the urine of males and females, support an overall correction factor of 0.7. Therefore, BCS proposes an AOEL of 0.01 mg/kg bw/day.	June 2005: See comments on open points 2.1 and 2.4. The lowest NOAEL (1.45 mg/kg bw/d) is found in the 1-year oral toxicity study in dogs. Since this is considered a short-term study, this NOAEL is suitable as a starting point for derivation of the AOEL. See also addendum. AOEL is set at 0.009 mg/kg bw/d.	EPCO 28 (27.06. – 01.07.2005): AOEL of 0.009 mg/kg bw/day confirmed by expects including an of oral absorption correction factor of 0.65 giving an overall factor of 154). Open point closed.

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	Open point 2.11: The dermal absorption value to be confirmed at the expert meeting as well as the scientific value of the rhesus monkey study. (see reporting table 2(17))	BCS supports the dermal absorption value of approx. 2% as derived from the monkey study. We consider the monkey dermal penetration study as appropriate; it was performed as an EPA requirement for the spirodiclofen registration in USA and was subsequently submitted in EU as well. Monkey studies are explicitly mentioned in the EU Guidance Document on Dermal Absorption (Sanco/222/2000 rev. 6 (2002)), where they are described as giving the closest values to human data. Our data were used without further correction by *in vitro* data. - We cannot follow the UK comment that the use of the monkeys is inappropriate since the monkeys (in contrast to rats) are not sacrificed after the study.	June 2005: See comments in reporting table on 2(17), 2(18), 2(19) and 2(20). September 2006: The RMS reassessed the study and concluded that the assumption of the experts in the meeting (namely that the study was performed with the concentrate, not with the spray), is not valid. The applied concentration and area dose is representative for the spray dilution, hence the RMS proposes a dermal absorption of 10% for both the concentrate and the spray dilution (see addendum).	EPCO 28 (27.06. – 01.07.2005): 3. The experts discussed the validity of the monkey study and determined a value of 10% for the concentrate based on the physical chemistry properties (kow >5), supported by the monkey. 4. A value of 65% was proposed for the dilution based on f the oral absorption value. Open point closed.
	Open point 2.12: The operator exposure to be discussed at an expert meeting. The RMS is asked to present the results of the estimations in relation to the systemic AOEL in the addendum. (see reporting table 2(21))	See separate BCS **position paper 2_12** (Wicke, H., 2004; BCS Document no MO-05-006760) which is based on BCS´s proposed AOEL of 0.01 mg/kg bw/d, a correction factor of 70% bioavailability and a dermal absorption of 2%.	June 2005: Regarding the comments on the sprayed area (knapsack, UK POEM): the note in the DAR is not correct and should read: 'Assuming a tank volume of 15 L, the treated area will be 0.15-0.45 ha (15 L x 30 operations /1000 or 3000 L/ha)'. This shall be taken into account in a revised DAR.	EPCO 28 (27.06. – 01.07.2005): Operator exposure to be recalculated. See 2.1. Open point still open. Evaluation meeting (4-6.12.2006) Operator, worker and bystander exposure was recalculated, showing exposure levels below the AOEL for mechanical and manual upward spraying in pome fruits,

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	continued Open point 2.12: The operator exposure to be discussed at an expert meeting. The RMS is asked to present the results of the estimations in relation to the systemic AOEL in the addendum. (see reporting table 2(21))		The RMS is of the opinion that the AOEL, dermal absorption, and exposure values have not changed considerably; therefore no recalculation of the risk assessment was considered necessary at this point. September 2006: Recalculations of the operator, worker and bystander exposures and the risk assessments were provided in the revised addendum. Open point considered closed.	stone fruits, citrus and grapes using the German model (operator, with the use of PPE) and EUROPOEM 2002 data (worker and bystander) Open point closed
2.1	Notifier to submit historical control data to make an additional evaluation of the renal cortical vacuolation in males possible. (see reporting table 2(31))	The historical control data were submitted on March 9, 2005. They show that the incidences of adrenal cortical vacuolation seen at 100 and 500 ppm in male rats are covered by the historical control data.	June 2005: See addendum. The submitted data indicated that the observed adrenal vacuolation in males at the lowest two dose levels (100 and 500 ppm) was within the historical data. Since no historical data for females was presented, the NOAEL was changed to 8.1 mg/kg bw/d, based on adrenal vacuolation in females at 500 ppm and above.	EPCO 28 (27.06. – 01.07.2005): Data requirement closed.

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	Open point 2.13: RMS to transfer the information (effects chronic feeding study rats) in column 3 of the reporting table to an addendum to be discussed at an expert meeting. (see reporting table 2(33) and 2(11))	See comments under Open Point 2.6.	June 2005: See addendum. More detailed information on weights of several organs were included, However, the NOAEL of the study was not changed.	EPCO 28 (27.06. – 01.07.2005): Open point closed.
	Open point 2.14: RMS to consider in a revised DAR/corrigendum DE comments on the additional drinking water limit in the DAR, Vol. 3, B.6.10.6. (see reporting table 2(46))		June 2005: The drinking water limit should not exceed the EU drinking water limit for pesticides of 0.1 µg/L and should not be more than 10% of the ADI. Since the EU limit is the lowest of these two, the EU drinking water limit for pesticides of 0.1 µg/L is applicable for spirodiclofen, as indicated in the DAR. We admit that the wording could have been clearer.	EPCO 28 (27.06. – 01.07.2005): Open point closed.
	New open point 2.15: RMS to revise the list of end points according the amendments proposed by EPCO 28.		September 2006: List of endpoints is revised. Open point considered closed.	EPCO 28 (27.06. – 01.07.2005): Open point still open. Evaluation meeting (4-6.12.2006) The list of end points was revised. Open point closed

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	Message from EPCO 30 to experts of the sections ecotoxicology and mammalian toxicology: To confirm that new specification from full-scale production is acceptable.		September 2006: It was concluded that the toxicological profile of spirodiclofen did not change with the new production process; see for the evaluation the revised addendum (B.6.8.1.3). Open point considered closed.	
	Added by RMS, as it was only mentioned in the discussion table, and not copied to evaluation table: Metabolites M01-M16 are toxicologically relevant. The RMS is to clarify whether BAJ 2740- dihydroxy and BAJ 2740-ketohydroxy are rat metabolites.		September 2006: BAJ2740-ketohydroxy and BAJ2740-dihydroxy do not appear in the rat. Predicted environmental concentrations in groundwater (PECgw) are equal to or less than 0.001 ug/L, hence these metabolites are not considered toxicologically significant. Open point considered closed.	Evaluation meeting (4-6.12.2006) BAJ2740-ketohydroxy and BAJ2740-dihydroxy are not rat metabolites.
	Transferred from section 1, open point 1.3: To address the toxicological relevance of the impurity BAJ 2740-Enol.			Evaluation meeting (4-6.12.2006) As spirodiclofen is proposed for classification as R40, all rat metabolites of spirodiclofen (e.g. BAJ 2740-enol) are considered toxicologically relevant.

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	New open point 2.16 (added by RMS): Evaluation of the full scale specification.		April 2009: In the DAR the production process of pilot batches and the pilot plant specification have been evaluated. At the end of the peer review process, information became available on the full scale production batches. The full scale production resulted in three new impurities. For mammalian toxicology, an evaluation of the full scale specification has already been performed, but this has not yet been peer reviewed. See the final addendum from November 2006, and specifically the Chapter with the revised addendum B6 B7 from September 2006, B.6.8.1.3 (Toxicological assessment of the new proposed specification), page 56-58. The argumentation provided by the notifier on the toxicological equivalence of the new production process is considered acceptable.	PRAPeR 69 (4 – 9 May 2009): Open point fulfilled Experts considered that the new specification form full scale production is acceptable

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	New open point 2.17 (added by RMS): Evaluation of the developmental neurotoxicity (DNT) study and the supplementary DNT study.		April 2009: In the final addendum from November 2006, in the Chapter with the revised addendum B6 B7 from September 2006, a DNT study has been evaluated, but this has not yet been peer reviewed. See B.6.7 (neurotoxicity), page 49-53. Subsequently, in order to address specific questions by EPA and PMRA, the notifier repeated parts of the DNT study. The RMS recently received the new study (d.d. 01-08-2008) which is evaluated in the addendum from April 2009. No neurodevelopmental effects were observed in these studies.	PRAPeR 69 (4 – 9 May 2009): Open point fulfilled. The experts concluded that there were no developmental nerotoxicology effects and the NOAEL can be set as 1500 ppm (119 mg/kg bw/d).

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	New open point 2.18 (added by RMS): The dermal absorption values and the revised risk assessment to be confirmed at the expert meeting.		April 2009: The RMS recently received new dermal absorption data (d.d. 26.11.2008) which is evaluated in the addendum from April 2009. Taking all dermal absorption data into account, the RMS proposes a dermal absorption value of 0.4% for the concentrate and 3% for the spray dilution. Because new dermal absorption values are proposed based on the new dermal absorption data, a revised risk assessment is performed in the addendum from April 2009, resulting in safe uses for the operator, bystander and worker.	PRAPeR 69 (4 – 9 May 2009): Open point fulfilled. Experts agreed to the proposal of the RMS.

1. Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.6.12, Dermal absorption, page 16	DE: The *in vitro* dermal absorption study must have been conducted with [^{14}C]-spirodiclofen, not with [^{14}C]-triflumizole.	
(2)	Vol. 3, B.6.12, Dermal absorption, page 17	DE: The total % non absorbed for the high dose on human skin should be 105.11, not 105.44 which is the total recovery in this experiment.	