PEER REVIEW REPORT ON **PICLORAM** 25 11 2009

TABLE OF CONTENTS

	Document	**File Name**
00	Cover page	00 picloram cover
01	**All comments received on the DAR**	**01 picloram all comments**
02	Reporting table all sections	02 picloram rep table rev 1-1
03	All reports from PRAPeR Expert Meetings	03 picloram all reports.
04	Evaluation table	04 picloram eval table rev 2-1

Comments on the Draft Assessment Report on picloram (EAS)

RMS UK

End of commenting period: 23 November 2007 (MS, NOT)

Date	Supplier	File
23.11.2007	France	01 picloram comments FR 2007-11-23 (revised).doc
23.11.2007	Notifier	02 picloram comments NOT 2007-11-23.doc
26.11.2007	Germany	03 picloram comments DE 2007-11-26.doc
03.12.2007	Austria	04 picloram comments AT 2007-12-03.doc
13.01.2009	EFSA	05 picloram comments EFSA 2009-01-13.doc

section 1 - Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis (B.1-B.5)

1. Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis (B.1-B.5)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1 lev1 1.5.3.1 LoEP summary of representive uses Vol.3 B3.2.4 application rate Vol.3 B3.2.5 Concentration of active usage	FR: Unit of the application rate is different in the different tables (g/ha or kg/ha) Please RMS correct.	
(2)	Vol.3 B.2.1.11	FR: The explanation given for the non-determination of solubility in water at pH 5,7 and 9 was not clear. Could RMS clarify.	
(3)	Vol.3 B.2.1.18	FR: Due to the structural formula of the active substance (an amino acid like) FR is of the opinion that another pKa (NH3+/NH2) should be investigated.	
(4)	Vol.3 B.2.2.15 Vol.3 B.2.2.16	FR: The determination of relevant impurities after storage was not reported. FR is of the opinion that this data is required.	
(5)	Vol.3 B.2.2.18 persistent foaming	FR: Only level of foam after 12 minutes was reported. FR is of the opinion that level of foam after other time should be reported.	
(6)	Vol.3 B.5.1.2 impurities	FR: FR is of the opinion that the method of determination of relevant impurity Hexachlorobenzen in technical material must not be classified as confidential and should be reported in B5 part.	
(7)	Vol.3 B.5.1.3 Plant protection product	FR: FR is of the opinion that the method of determination of relevant impurity Hexachlorobenzen in PPP must be submitted.	
(8)	Vol. 4 C.1.2 c) analytical profile of batches	FR: The given certified values are not relied on with batches but RMS explained that a justification was given in the form of statistical analysis over a long period. Could a Summary of those statistical analyses be reported in volume 4. For transparency, could RMS precise the year of fabrication of the 7 batches used for batch analysis.	

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section 1 - Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis (B.1-B.5)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(9)	Vol. 4 C.1.4.1 a) organic impurities	FR: The method used for determination of impurities in technical material is a HPLC-DAD with detection at 225 nm. This method cannot be considered specific as detection is only performed at one wavelength and not on full scan. Could RMS clarify.	

section 3 - Residues (B.7)

3. Residues (B.7)

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.7.1.1, p. 155 Metabolism, distribution and expression of residues in plants – Oil seed rape	FR: Table B7.2: plotting %TRR 8.9 and 32.8, the sum is not 36.8 but 41.8 ; are these values correct? Also, only in the acetonitrile/water extract with the TLC mehod, the sum of %TRR is 100% (picloram + conjugates); how can we explain 32.8% TRR in the diethyl ester extract after hydrolysis?	
(2)	Vol. 3, B.7.1.1, p. 155 Metabolism, distribution and expression of residues in plants – Oil seed rape	FR: Could RMS please clarify “Ca 97% of this released radioactivity was identified as unchanged picloram.” (text following table B7.2)	
(3)	Vol. 3, B.7.1.3, p.159 Metabolism, distribution and expression of the residue in rotational crops	FR: the rate applied of 0.583 kg/ha does not correspond to 285N as the GAP states 0.02345 kg/ha. This rate corresponds to about 25N.	
(4)	Vol. 3, B.7.1.4, p.166 Metabolism in plant – Summary/assessment	FR: “Crops were treated with picloram labelled in the 2,6 position of the ring at exaggerated dose rates”. 1.7N is not really an exaggerated dose rate for oilseed rape; moreover no rate (GAP) was determined on wheat so this dose is not exaggerated.	
(5)	Vol. 3, B.7.1.4, Metabolism in plant – Summary/assessment	FR : see remark (1)	
(6)	Vol. 3, B.7.1.4, p.168 Summary, assessment	FR: the treatment rate used in this study is of 25N and not of 285N.	as the treatment rate used in this study is 25N instead of 285N and considering the results of analysis could be linear, the maximum rates found in samples and re-calculated at the 1N dose, are at detectable levels (>0.01 mg/kg). Thus, detectable residue levels could occur in rotational crops. A field study should be submitted.

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section 3 - Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(7)	Vol. 3, B.7.2.2, p.169 Goats	FR: please explain how RMS obtained the 1N dose of 0.003 mg/kg diet for goats	
(8)	Vol. 3, B.7.2.3, p.173 Poultry	FR: please explain how RMS obtained the 1N dose of 0.001 mg/kg diet for poultry	
(9)	Vol. 3, B.7.2.10, p.189 Residues in succeeding or rotational crops	FR : see remark (3) and (6)	

section 4 - Environmental fate and behaviour (B.8)

4. Environmental fate and behaviour (B.8)

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.8.1.4 Field studies Field dissipation a) (Knowles, S., Unsworth, C., 2003)	FR: The RMS judged that the regression used by the notifier to estimate the DT50 is not reliable. However, the DT50 founded is reported in the endpoints. Please clarify why a DT50 calculated with an unreliable regression is accepted?	
(2)	Vol. 3, B.8.1.3 Photolysis in soil (Fontaine, D.D., Woodburn, K.B., 1986)	FR: The RMS judged that the light source was not acceptable in the photolysis soil study because as it is referred in the OCDE guidelines a xenon lamp must be used. A photolysis study with a xenon lamp should be done.	
(3)	Vol. 3, B.8.4.3 Ready biodegradation (Heim, D., Heim, L;, 2002)	FR: It seems that results with picloram and sodium benzoate are not indicated.	
(4)	Vol. 3, B.8.4.4 Water/sediment studies (Yoder R.N., Meilt, T.J., 2004)	FR : Can you clarify the values used in the paragraph just before the table B.8.56 which begin with : ”The aerobic aquatic degradation of Picloram led to the formation of two degradates >10%. …”. Indeed, in the first sentence, the RMS is talking about %AR in the whole system whereas in the second sentence, he is talking about %AR in water and in sediment. What’s more the concentration in water and in sediment refer to average values of the table B.8.58 which is not clear at first sight.	
(5)	Vol. 3, B.8.4.4 Water/sediment studies (Yoder R.N., Meilt, T.J., 2004)	FR: Can you please clarify why do you use a DT50 water of 300 d and a DT50 sediment of 196.1 d whereas in the table B.8.59 the maximal value for the DT50 water is 135 and the maximal value of DT50 sediment is 256.6.	

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section 4 - Environmental fate and behaviour (B.8)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(6)	Vol. 3, B.8.6 Predicted environmental concentrations in surface water and groundwater (PECsw and PECgw)	FR: For the chemical specifics input parameters for Step 1 and Step 2 of the metabolites, can you explain why input values of aminopyralid are used?	
(7)	Vol. 3, B.8.6 Predicted environmental concentrations in surface water and groundwater (PECsw and PECgw)	FR: Can you clarify why the DT50 soil of 3,6-dichloro analogue and 5,6-dichloro analogue is 12.1d?	

5. Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)		FR : Note that DAR is clear and very easy to read!	
(2)	Vol. 3, B.9.1.1.1: Active substance ii)	FR: Typographic error: There is a repetition of the sentences “No mortalities occurred…at any dosage tested”.	
(3)	Vol. 3, B.9.2.2.2: Hazard Classification/Labelling of plant protection products	FR: We agree with the classification of plant protection product. Could you clarify the effects on the survival of juvenile fish by referring to table B.9.21.	
(4)	Vol. 3, B.9.2.3.1 Fish early life stage toxicity/Fish life cycle test/Chronic toxicity test on juvenile fish b) Metabolites Vol.3, B.9.2.3.5 Effects on aquatic plants b) Metabolites	FR: Typographic error: Note that some concentrations are given in mg a.s/L instead of mg XDE750./L.	
(5)	Vol.3, B.9.2.3.3 Table B.9.26 : Emergence and development data	FR: Typographic error: The lowest concentration is **6.3** instead 63 mg a.e/L.	
(6)	Vol.3, B.9.2.4.1 b) Metabolites	FR: It was said that there were 2 degradation products which occurred at >10 % AR in the water/sediment study. However, the 3,6-dichloro analogue (XDE 750) reached a maximum of 8.7% AR in the aqueous phase and 4.6 % AR in the sediment. Please correct this contradiction.	
(7)	Vol. 3, B.9.2.4.1 b) Table B.9.31: Summary of acute aquatic toxicity endpoints for the metabolite XDE-750	FR: The 72 h EbC50 for *Navicula pelliculosa* are **19** (nominal) and 18 (mean measured) mg XDE 750/L.	

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section 5 - Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(8)	Vol. 3, B.9.6.3.1 Active substance/plant protection product Table B.9.45: TERa values for earthworms based on studies using technical picloram and the formulated product 'GF-224'	FR: When corrected for the test substance purity, the 14-day LC50 value from the acute study using technical picloram is 4475 mg a.s./kg soil. In the table B.9.45, the TERa value is not based on the corrected LC50 value. Please modify the TERa value.	

6. Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis (B.1-B.5)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, Appendix 3, Listing of End points, page 51, Vapour Pressure	DAS: Vapor pressure should be 8 x 10^{-8} Pa at 25°C (99.4%), not 8.00 x 10^{-8} Pa at 25°C (99.4%),	Significant figures should be 1
(2)	Vol. 1, Appendix 3, Listing of End points, page 51, Solubility in water	DAS: Temperature should be 20°C, not 25°C	
(3)	Vol. 3, B.2.1.5, vapour pressure	DAS: Vapor pressure should be 8 x 10^{-8} Pa at 25°C (99.4%), not 8.0 x 10^{-8} Pa at 25°C (99.4%),	Significant figures should be 1
(4)	Vol. 3, B.2.1.6, Volatility, Henry's law constant	DAS: spelling error - should be /mol at, not /molat	Spelling error
(5)	Vol. 3, B.2.1.13, Partition co-efficient	DAS: pH buffer $\log_{10}P_{OW}$ should = 0.057 to 0.248, not -0.057 to 0.248	
(6)	Vol. 3, B.2.2.9, Acidity / alkalinity	DAS: Add to reference Author of Comb, A.L. 2004 for reference to pH (neat): 7.3 at 20°C	Roulin, S. references the pH of the neat formulation as 7.24.
(7)	Vol. 3, B.2.2.13, Relative Density	DAS: Reference should be changed to Comb, A.L. 2004, not Roulin, S. 2001	Roulin, S. references the relative density to be 1.1688.

7. 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, Table B.6.2.5; Eye irritancy. P76, Table B.6.8	DAS: The mean score for corneal opacity presented in Table B.6.8 should be 0.11, not 0.33	
(2)	Vol. 3, B.6.6.3a; 28-day dog study: summary of findings. p. 84, Table B.6.13	DAS: In Table B.6.13, liver weight for control females should correctly be 211.7, not 311.7	
(3)	Vol. 3, B.6.3.3b; Oral Short-term toxicity in the dog. P. 85	DAS: Last line under "Bodyweights and food consumption" should read "lower in these groups" not "lower in theses groups"	
(4)	Vol.3, B.6.4.1b Genotoxicity in vitro: CHO/HGPRT assay. P. 94	DAS: Line 5 should read "five concentrations between 250-1250 µg/mL", not "five concentrations between 250-1000 µg/mL".	

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(5)	Vol.3, B.6.5.1b Chronic toxicity and carcinogenicity in the rat. P. 100-101.	DAS: The submitted studies show that Picloram is not carcinogenic in rats or mice. The DAR notes '*some evidence of carcinogenicity…with a slightly increased incidence of hepatocellular adenoma in top dose females*' (500 mkd; Cosse et al., 1992). However, incidences were 2%, 2% and 6% in control, low and high dose groups, not statistically significant, within historical control range for the lab (0 to 8%) and without any pre-neoplastic liver lesions. This is normal variation, unrelated to treatment..	The benign liver adenomas observed in female rats in this study represent normal variability of a commonly occurring spontaneous tumor type within this colony of Fischer 344 rats. The range for this finding in control female Fischer 344 rats from this laboratory was 0/50 – 4/50 for 14 studies performed from 1987 to present. Further supporting that this observation was not related to the administration of Picloram, two benign liver ademonas were observed in the control female group of the other rat carcinogenicity study submitted (Landry *et al.*). Based on the lack of statistical significance and spontaneous occurrence of this tumor type, the Notifier does not believe that this finding is related to administration of Picloram and therefore requests that statements indicating "evidence of carcinogenesis" be removed from the draft assessment report. NOTE: The increase in "neoplastic nodules" in female rats reported in the NTP study mentioned in the DAR can not be clearly interpreted since this category potentially included non-tumorous lesions in addition to benign liver tumours. (Maronpot, *et al.*). The dosing regime was also altered mid-study, further complicating any conclusion of treatment related effects and raising concerns that the originally selected doses were excessively toxic. The Notifier submits that this study is of questionable quality and provides little value in an overall assessment of the carcinogenic potential of Picloram. Reference: Maronpot, R.R., et al. (1986). National Toxicology Program Nomenclature for hepatoproliferative lesions of rats. Toxicol. Pathol. 14, 263-273.

section 2 - 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
(6)	Vol.3, B.6.6.1 Multi-generation study in the rat. P. 109, Table B.6.25	DAS: Values for conception index for F0 males and females were switched in Table B.6.25. Male values should be: 89.7, 96.6, 86.2, 92.3; Female values should be: 86.7, 96.6, 83.3, 90.0.	
(7)	Vol.3, B.6.6.2a Developmental toxicity in the rat (K-salt), P. 111	DAS: The Notifier supports the proposed NOAEL of 1000mg/kg/d (Acid Equivalent of 860 mg/kg/d) and maintains that the increased incidence of excessive salivation was not toxicologically meaningful. Excessive salivation was observed only in developmental studies where Picloram was administered by gavage. The lack of similar observations in dietary studies with comparable or higher doses indicates that the effect can be attributed to gavage administration and is not the result of Picloram-mediated toxicity.	Excessive salivation seen in this and the rat developmental study using the TIPA salt of Picloram (Schroeder) was likely the result of these salts being administered by gavage. Salivation was also monitored as part of the 2nd 2 year rat study (Cosse *et al.*) and no increase in salivation was reported with dietary concentrations of Picloram up to 500 mg/kg. Increased salivation was observed with the TIPA-salt of Picloram at a dosage equivalent to 560 mg/kg/day Picloram. Since this approximates the dose of 500 mg/kg at which no increase in excessive salivation was observed in the 2 year dietary study, it is unlikely that increased salivation is toxicologically meaningful in either rat teratology study, but rather is attributable to differences in route of administration or physical properties of the substance (salts versus acid). In addition, no excessive salivation was reported in a multi-generation study in rats (Breslin *et al.*) receiving dietary Picloram up to 1000 mg/kg/day. The lack of excessive salivation in dietary studies with Picloram acid demonstrates that this effect is not a direct result of Picloram toxicity. Therefore, a clear maternal NOAEL can be established at 1000mg/kg/day in this study.

section 2 - 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
(8)	Vol.3, B.6.6.3a Developmental toxicity in the rabbit (K-salt), p. 115	DAS: The Notifier affirms that the NOAEL for developmental effects should be set at 400 mg/kg (Picloram Acid Equivalents). The foetal alterations observed at the top dose of this study did not differ statistically from control. The two incidences of forelimb flexure were limited to a tendon anomaly and importantly were confined to a single litter. The high-dose findings were not observed in the rabbit teratology study with the bioequivalent TIPA salt or in any other developmental study with Picloram.	The two Picloram salts (Potassium and TIPA) are recognized to be toxicologically equivalent to Picloram acid. In the rabbit teratology study utilizing the TIPA salt, animals received doses up to 558 mg/kg of Picloram (acid equivalents) which is higher than the top dose in the study utilizing the potassium salt form of Picloram (400 mg/kg). The lack of similar foetal alterations in the rabbit teratology study utilizing the TIPA salt is further evidence that these effects are spurious in nature and are not the result of Picloram administration.
(9)	Vol. 3, B.6.6.3b Developmental toxicity in the rabbit (TIPA salt), p. 118, Table B.6.29	DAS: Table B.6.29 indicates 2 total resorptions each at 538 mg/kg/d and 1000 mg/kg/d; there were no litters totally resorbed in this study.	

section 2 - 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
(10)	Vol. 3, B.6.6.3b Developmental toxicity in the rabbit (TIPA salt), p. 120	DAS: A maternal NOAEL of 180 mg/kg/d (Acid Equivalent of 100 mg/kg/d) is supported by only limited effects on maternal body weight gain at this dose. A modest decrease in body weight was observed only at the day 7-10 interval and was due to decreased food consumption. The effect was minimal, corresponding to less than a 1% change in body weight. This minor effect was also transient with no overall negative impact on body weight or weight gain at study termination. No clinical or other findings indicative of toxicity were reported for animals treated with 180 mg/kg Picloram TIPA-salt.	For the weight gain decrement observed to be biologically meaningful, one would expect the effect to be observed through the majority of the study. This is not the case since weight gain for the 100 mg ae/kg treated animals was in fact greater than that for control treated animals at each subsequent interval in the study (phase 2). Clearly any treatment related effect at this early time point was transitory in nature allowing for rapid and complete adaptation by the next time interval. The Notifier concludes that the observed effect on body weight gain was not toxicologically meaningful due to the mild nature (<1% change) and transient duration (only observed at one interval) of the observation.
(11)	Vol. 3, B.6.10 Summary of mammalian toxicology and proposed ADI, AOEL, ARfD and MAC, p. 125	DAS: First line under Short-term toxicity: add comma after the word “rat”.	

section 2 - 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
(12)	Vol. 3, B.6.10.1 Acceptable Daily Intake (ADI), p. 130	DAS: The Notifier supports the proposed ADI of 0.35 mg/kg derived from the NOAEL of 35 mg/kg/day in the 1 year dog study. This exposure limit is based on the most suitable toxicological endpoint available and is health protective. The Notifier does not agree with using the rabbit developmental study and its corresponding NOAEL to set the ADI: 1.) A transient reduction in weight gain at an early time-point is not justifiable rationale for setting an ADI. 2.) The Notifier supports a maternal NOAEL of 100 mg/kg in the rabbit developmental toxicity study (point #10); therefore 35 mg/kg is the lowest NOAEL and should be used to derive the ADI.	The Notifier maintains that the 1-year dog study and its accompanying NOAEL are more appropriate for deriving a chronic ADI than use of a developmental toxicity study in which there was a small, transient reduction in weight gain at only one time interval throughout the study which likely resulted from a decrease in food intake following gavage exposure. Such a limited and transient effect using this study design and length is inappropriate when approximating chronic dietary exposure in humans. The Notifier has addressed this point (#10) and does not believe this effect to biologically meaningful and therefore does not agree with the RMS supported NOAEL of 30 mg/kg/day. The lowest NOAEL is therefore 35 mg/kg/day and this value should be utilized in establishing the ADI.

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section 2 - 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
(13)	Vol. 3, B.6.10.2 Acute Reference Dose (ARfD), p. 130	DAS: The Notifier maintains the active substance Picloram has low acute hazard potential (LD50 > 4000 mg/kg bw), is not teratogenic, and other toxicological alerts (FAO/WHO, 2000) that would trigger the establishment of an ARfD have not been demonstrated.	The Notifier recognizes WHO (2002) guidance which recommends the establishment of an ARfD for substances whose acute oral LD_{50} value is <1000 mg/kg bw. The LD_{50} for picloram is >4000 mg/kg bw and hence does not represent an acute hazard. For clopyralid, a similar pyridine herbicide, there was no ARfD established based on this same logic and the experts agreed. **NOTE:** In the DAR, B.6.10.2 (ARfD), the summary of findings notes that there was weight loss in the 6-month dog study as well as in the 1-yr dog study, which is inaccurate. There was decreased body weight gain (which is what the DAR reports in the study summary itself) in the 6-month study and similar findings in the 1-yr dog study, but the only occurrence of actual weight loss was limited to high-dose females in the 1-yr study from Days 0-7. The Notifier would draw the PSD's attention to this inaccuracy, which should be corrected as it serves as some of the PSD's basis for deriving an ARfD. In those cases where there are hazard data available that would justifiably warrant the development of an ARfD, a developmental toxicity study is typically not appropriate as it involves an exposure regimen (continuous daily exposure for a defined period) which is not suitable for approximating the true intent behind development of an ARfD – that of determining potential toxicity following a single daily dose. For Picloram, there is neither maternal nor developmental toxicity or a critical endpoint that was identified in the rabbit developmental toxicity study that would justify its use as the critical study upon which to base an acute reference dose. Throughout the toxicological database for Picloram, there is evidence from the animal studies that palatability of the technical material, as presented in diet, may influence (i.e., reduce) dietary intake, which in turn results in reduced body weight gains, albeit of varying degree. The relevance of this point is that because of the palatability of the material, there is decreased concern for acute overexposure which in turn lessens the need for an ARfD. The Notifier maintains that there is no need to establish an ARfD for picloram.

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section 2 - 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
(14)	Vol. 3, B.6.10.3a Admissible Operator Exposure Level (AOEL), P. 131	DAS: The Notifier maintains that the systemic AOEL is appropriately based on the maternal NOAEL for the rabbit developmental study (TIPA salt). However, the Notifier does not agree with the NOAEL of 30 mg/kg/d and maintains that the NOAEL was clearly and firmly established at 100 mg/kg/d (point #10) resulting in an AOEL of 1 mg/kg/day.	In 'Guidance for the setting of Acceptable Operator Exposure Levels (AOELs)' Commission draft working document 7531/VI/95 rev.6, 2001), it is proposed that an AOEL should be established for an exposure period appropriate to the duration of exposure of the operator to the product in question. For GF-224, there will be only one application per crop per year, for treatment of broad-leaf weeds during the Spring. Therefore, exposure to Picloram is only during a short-time period in any given year and will in fact be <28 days in any season. While the PSD and Notifier agree that the developmental rabbit study fulfils this requirement on a temporal level, the Notifier recognizes and supports a NOAEL of 100 as the basis for subsequent AOEL derivation. The basis and rationale for this NOAEL has been described above in the text (point #10) In summary, the Notifier maintains that the scientific weight of evidence and data from this study support a clear NOAEL of 100 mg/kg bw/day. The clear absence of other toxicological correlates at this dose level support the view that this dose level is not associated with any other significant or observable toxicity which is also consistent with the interpretation (i.e., not toxicologically significant) of the transient weight gain decrements in dams from GD 7-10.
(15)	Vol. 3, B.6.10.3b Admissible Operator Exposure Level (AOEL), P. 131	DAS: The Notifier does not support the establishment of a dermal AOEL since the systemic AOEL is intended to account for, and address, all routes of exposure	
(16)	Vol. 3, B.6.10.4 Maximum Allowable Concentration, P. 131	DAS: The Notifier accepts the default MAC of 0.1 µg/l	

section 2 - 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
(17)	Vol. 3, B.6.14 Operator and bystander exposure	DAS: no comments	

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section 3 - Residues (B.7)

8. Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, 2.4, Residues, Estimates of potential and actual exposures	DAS: As no Acute Reference Dose (ARfD) is required for picloram, the sentence 'The short term dietary intakes (NESTIs) for residues of picloram from the consumption of oilseed rape have been calculated for 10 consumer groups (UK diet). Based on acute exposure estimates for short term dietary exposure, intakes for all consumer groups are less than 1% of the ARfD of 0.3 mg/kg bw/day' should be removed.	
(2)	Vol. 1, Appendix 3, Listing of Endpoints	DAS: The entry for NESTI under Consumer Risk Assessment should be removed and replaced with 'n/a'.	
(3)	Vol 3 B.7.16.2.2, Short term intakes - National Estimate of Short Term Intake (NESTI)	DAS: As no Acute Reference Dose (ARfD) is required for picloram, the section B.7.16.2.2 should be deleted and replaced with the sentence: 'As no ARfD is set for picloram, an acute dietary risk assessment is not required and has not been performed'.	
(4)	Vol. 3, B.7.17, Summary and evaluation of residue behaviour	DAS: The sentence 'The short term dietary intakes (NESTIs) for residues of picloram from the consumption of oilseed rape have been calculated for 10 consumer groups (UK diet). Based on acute exposure estimates for short term dietary exposure, intakes for all consumer groups are less than 1% of the ARfD of 0.3 mg/kg bw/day' should be removed.	

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section 4 - Environmental fate and behaviour (B.8)

9. Environmental fate and behaviour (B.8)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, Level 2, 2.5.2, Fate and behaviour in soil	DAS: RMS commented that field studies for Poland and Germany are not accepted as may not be representative of degradation as showed significant residues in the lowest soil horizon. In addition studies were conducted at times of year when soil temperatures may have been warmer than notified GAP. See comments 2-5 for DAS clarification of position.	
(2)	Vol 3, B 8.1.4b, Field dissipation – Polish study	DAS: Add line in Table B.8.30 to note 0-90cm showed no soil residues in any horizon after 271 days (Polish trial site). This supports that there is little/no significant leaching to depth. The kinetics calculated from the Polish field study are therefore representative of the degradation of picloram under field conditions.	
(3)	Vol 3, B 8.1.4c, Field dissipation – German study	DAS: For this ^{14}C study add to DAR that at the bottom of these outdoor soil cores (20cm), all leachate was collected on a weekly basis. 111.5L was collected in total and no radioactivity was detected in the water on any occasion (see conclusion of report GHE-P-10611, ref K60). This clearly demonstrates that there was no leaching of picloram or any other ^{14}C material and therefore the kinetic analysis of the total radioactivity in soil represents a conservative estimate of the DT50. DT50 = 48.9 days	

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section 4 - Environmental fate and behaviour (B.8)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(4)	Vol 3, B 8.6, PEC surface water	DAS: RMS comment that field studies for Poland and Germany are not accepted as may not be representative of degradation as showed significant residues in the lowest soil horizon. In addition studies were conducted at times of year when soil temperatures may have been warmer than notified in the GAP. The data presented for lower horizon (0-90cm) for Poland and no leaching >20cm in the German study show that the degradation kinetics presented for the 4 EU field studies are representative of picloram degradation in the field. Furthermore, field standardisation for soil moisture and temperature as recommended by FOCUS allow any temperature differences in the GAP timing to be corrected. Field standardisation gives a DT50 = 8.7 days. Knowles, S.: Recalculation of Field Kinetics for Picloram using FOCUS Kinetics Methodology. Dow AgroSciences unpublished report GHE-P-11573, 02 April 2007 (see column 3 for report) This will not significantly impact PECsw	For confidentiality reasons the attachment has been removed by EFSA.

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section 4 - Environmental fate and behaviour (B.8)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(5)	B 8.6, PEC groundwater	DAS: RMS comment that field studies for Poland and Germany are not accepted as may not be representative of degradation as showed significant residues in the lowest soil horizon. In addition studies were conducted at times of year when soil temperatures may have been warmer than notified in the GAP. The data presented for lower horizon (0-90cm) for Poland and no leaching >20cm in the German study show that the degradation kinetics presented for the 4 EU field studies are representative of picloram degradation in the field. Furthermore, field standardisation for soil moisture and temperature as recommended by FOCUS allow any temperature differences in the GAP timing to be corrected. Field standardisation gives a DT50 = 8.7 days (see column 3 for report) This will significantly impact PECgw as it would allow annual applications to be applied instead of applications every 3 years as proposed in the DAR. The initial PECgw calculations which were submitted for the Annex II dossier used a DT50 = 30.5 days (non-standardised data, GHE-P-10687, ref MK02) so would represent a conservative assessment for PECgw using field DT50 values.	For confidentiality reasons the attachment has been removed by EFSA.

section 5 - Ecotoxicology (B.9)

10. Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	All sections in Vol. 3 B.9	DAS: No comment	

11. Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis (B.1-B.5)

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.2.1.1 boiling point	DE: Just for clarification, the given justification in the column "comment" is incorrect and not in compliance with the Directive 94/37/EC. However, there is no need to require any additional data.	
(1)	Volume 3, B 5.2, Volume 3, B 5.3.1, Volume 3, B 5.3.2	DE: It should be discussed in a meeting of experts, if confirmation by one additional GC-MS ion (isotopic peak of [M-HCl]) is sufficient.	
(2)	Volume 3, B 5.2	DE: Recovery and precision data of the confirmatory method (Hastings, 2003 a) should be presented in an addendum. Justification: "GC-MS is considered to be highly specific provided … fragment ions … were used for …quantification" (SANCO 825).	
(3)	Volume 3, B.5.3.1, Volume 3, B.5.3.2	DE: Just for clarification, validation data are presented in table B.5.2 (and not in B.5.3 as written).	
(4)	Volume 3, B.5.3.1	DE: Recovery and precision data of the confirmatory method (Hastings and Scheuermann, 2001 a) should be presented in an addendum. Justification: "GC-MS is considered to be highly specific provided … fragment ions … were used for …quantification" (SANCO 825).	

section 1 - Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis (B.1-B.5)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(5)	Volume 3, B.5.3.2	DE: Recovery and Precision data of the confirmatory method (Hastings and Scheuermann, 2001 b) should be presented in an addendum. Justification: "GC-MS is considered to be highly specific provided … fragment ions … were used for …quantification" (SANCO 825).	

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12. 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.6.2.3, Acute inhalation toxicity; Vol. 1, List of endpoints	DE: Only one study with the active substance is reported in which the maximum attainable concentration was extremely low. A further inhalation study with the potassium salt of picloram is mentioned elsewhere in the DAR suggesting that the LC_{50} was at least above 1.63 mg/L. For giving a more comprehensive picture, this value should be included in the endpoint list.	
(2)	Vol. 3, B.6.2.6, Skin sensitisation; Vol. 1, 2.1.4, Classification and labelling	DE: It should be considered and discussed on the PRAPeR meeting to allocate the risk phrase R43 and classify picloram accordingly as “irritant”. Justification: The current assessment is based solely on a (negative) Buehler test with 3 inductions that is usually regarded not sufficient to exclude a skin sensitising potential. Furthermore, evidence of sensitisation was found for the potassium and the TIPA salts and the isooctyl ester of picloram. For the proposed ARfD, e.g., studies with the salts have been taken into account.	

section 2 - 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
(3)	Vol. 3, B.6.5.1, Chronic toxicity and carcino-genicity in the rat	DE: In the elder study (Landry et al., 1986), the NOAEL is rather seen at the lowest dose of 20 mg/kg bw/day than at the mid dose level of 60 mg/kg bw/day. At this latter dose level, there were still significant increases in various histopathological findings in liver and pancreas.	
(4)	Vol. 3, B.6.10.1, ADI	DE: A slightly lower ADI of 0.2 mg/kg bw instead of 0.3 mg/kg bw is proposed. Justification: Usually, an ADI should be based on a long-term study. In case of picloram, the first study in rats employing rather low dose levels is considered the most suitable basis. Since the NOAEL in this study is seen at 20 mg/kg bw/day (see comment above), a numeric value of 0.2 mg/kg bw/day would result.	
(5)	Vol. 3, B.6.10.2, ARfD	DE: The need of and, if needed, the most appropriate basis for setting an ARfD should be discussed on the PRAPeR meeting.	
(6)	Vol. 3, B.6.10.3, AOEL	DE: Based on the NOAELs of 35 mg/kg bw/day in the 6-month and 1-year dog studies, a slightly higher value of 0.35 mg/kg bw/day instead of 0.3 mg/kg bw/day is proposed. Justification: If available (and, thus, the situation is different from ARfD setting), it is preferred to use studies that were performed with picloram itself and not with its salts as basis for setting reference values.	

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section 2 - 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
(7)	Vol. 3, B.6.10.3, AOEL	DE: A need for setting an additional dermal AOEL is not seen.	
(8)	Vol. 3, B.6.10.12, Dermal absorption	DE: It is very unlikely that dermal absorption of the dilution was in fact by 30 times lower than that of the concentrate. Taking into account the human volunteer study, it is suggested to use a 3% estimate for both the concentrate and the formulation. This approach might cover a worst-case assumption but should be subject to PRAPeR meeting discussion.	
(9)	Vol. 3, B.6.14.1, B.6.14.2 and B.6.14.3, operator exposure, bystander exposure and worker exposure	DE: On the basis of the proposed AOEL [c. f. comment (6)] as well as on the basis of the suggested dermal absorption (if applicable) the data should be re-calculated.	

13. Ecotoxicology (B.9)

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.9.3.2, Risk assessment for mammals	DE: The acute and long-term endpoints for mammals used for risk assessment in the German national authorisation (acute oral LD_{50} = 3563 mg as/kg bw, NOEL (rabbit) = 40 mg as/kg bw/d) are lower than the endpoints used in the DAR (acute oral LD_{50} = 4012 mg ae/kg bw, NOEL (rat) = 1000 mg as/kg bw/d; ae = based on acid equivalents). This might result in unacceptable risk and should therefore be clarified.	

14. Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis (B.1-B.5)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, LOE minimum purity	AT: The upper and lower limit of the TK should be inserted.	
(2)	Vol. 1, LOE analytical methods-plant matrices	AT: The matrix grass should be deleted as no MRLs are proposed.	
(3)	Vol. 1, LOE analytical methods-soil	AT: It should be indicated that the GC-MS method refers to the active substance and the LC-MS/MS method to the metabolite.	
(4)	Vol. 1, LOE analytical methods-water	AT: It should be indicated that the GC-MS method refers to the active substance and the LC-MS/MS method to the metabolite.	
(5)	Vol. 3, B.2.1.11 solubility in water and B.2.1.13 partition coefficient	AT: Was the effect on pH decreasing observed for log Pow determination as well?	
(6)	Vol. 3, B.3.5.2 Procedures for cleaning application equipment	AT: The efficacy should be demonstrated.	
(7)	Vol. 3, B.5.2 method 2 (GRM 00.19) plants	AT: A confirmatory technique is required since only 2 fragmentations > m/z 100 are used for quantification and confirmation.	

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section 1 - Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis (B.1-B.5)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(8)	Vol. 3, B.5.3.1 method 1 (GRM 00.18) soil	AT: A confirmatory technique is required since only 2 fragmentations > m/z 100 are used for quantification and confirmation.	
(9)	Vol. 3, B.5.3.2 method 1 (GRM 00.17) water	AT: - A confirmatory technique is required since only 2 fragmentations > m/z 100 are used for quantification and confirmation. - The reported linearity range does not cover the range of fortifications unless dilutions of the samples have been performed. Clarification is requested. - The characteristics of surface water are missing.	
(10)	Vol. 3, B.5.3.3 method 1 (GRM 02.29) air	AT: The reported linearity range does not cover the range of fortifications unless dilutions of the samples have been performed. Clarification is requested.	
(11)	Vol. 4, C.1.2 c) analytical profile of batches	AT: The justification of the notifier accepted by RMS for higher specification of the impurity or impurities (?) should be presented in an addendum. In addition to impurity *4-Aminotet* the specification of the impurities *6 Isomer* and *6-OH TA* has to be clarified. For the impurities *Guanidine*, *4 DCT*, *Amide* and *tet acid* a justification for specification should be presented as it is not supported by batch analyses (all are <1g/kg).	

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section 1 - Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis (B.1-B.5)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(12)	Vol. 4, C.1.3 composition of the PPP	AT: The contents of the active substances should be expressed as the corresponding salts.	
(13)	Vol. 4, C.1.4.1 analytical method - impurities	AT: Since no information concerning initial identification of the impurities is given in 1.10 confirmatory techniques are required.	

section 2 - Mammalian toxicology (B.6)

15. 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

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section 3 - Residues (B.7)

16. Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

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section 4 - Environmental fate and behaviour (B.8)

17. Environmental fate and behaviour (B.8)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

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section 5 - Ecotoxicology (B.9)

18. Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

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19. Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis (B.1-B.5)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 4, Table C.1.3. Analytical profile of batches p.8	EFSA: the manufacturing date of the 7 batches is missing	
(2)	Vol. 4, Table C.1. Technical specification for impurities p.4 and Table C.1.3. Analytical profile of batches p.8	EFSA: the specification of the impurities not entirely supported by the batch data, it is not clear what was the basis of the specification for impurity 6 Isomer or the impurities found below 0.1 % in all batches (Guanidine, 4DCT, 4-aminate, 4-aminotet, amide, tet acid, 6-OH). If a justification was provided and the specification set based on QC data, EFSA would welcome a summary of the information presented as it was agreed on PRAPeR 21	
(3)	Vol. 4, Table C.1. Technical specification for impurities p.4 and Table C.1.3. Analytical profile of batches p.8	EFSA: RMS clarified what happens with batches out of specification in case of impurity sulfuric acid, we assume that the same is valid for the relevant impurity HCB too, which also exceeds the specification in one of the batches (QK07162951)	

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(4)	Vol. 4, Table C.1.3. Analytical profile of batches p.9	EFSA: can we assume that quantification by internal or external standardisation means that the quantification was done using the analytical standards of the individual impurities, meeting at least the agreement during PRAPeR 36 meeting: *"Specificity of the analytical method for the determination of the impurities in the active substance as manufactured (requirement 4.1) can be suitably addressed by retention time match with reference standards.* *Confirmation of identity of impurities should be addressed under section 1.10/1.11"* No information is available about this confirmation.	
(5)	Vol. 4, C.1.4.1 Methods of analysis for impurities p.11	EFSA: the LOD for the HCB method is not mentioned	
(6)	Vol. 4, Table C.1. Technical specification for impurities p.4 and Table C.1.2. Identity of impurities p.7	EFSA: in the case of the relevant impurity HCB there is a discrepancy between the values presented in the tables C.1 and C.1.2	
(7)	Vol. 4, C.1.4.1 Methods of analysis for impurities p.11	EFSA: it is not clear which was the method used for the a.s. determination in the 5 batch analysis, was it the method used for the determination of the impurities?	

section 1 - Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis (B.1-B.5)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(8)	Vol. 1, GAP table, p.10, Vol.3, GAP table, p.35, Vol.3, B.3.2.5 Conc. of a.s in material used, p.39, Vol.1, 1.5.3.3 p.12 Vol.1, LoEP, p.53	EFSA: clarification is needed concerning the values and/or units for the concentration of the active in the diluted spray is 0.02345 kg/L and the ones in the GAP tables. The unit in Vol. 3 is g/ha, while in Vol. 1 kg/ha. Taking the value of 23.45 g picloram/ha and 100L/ha water, the used concentration would be 0.2345 g/L	
(9)	Vol. 1, GAP table, p.10, Vol.3, GAP table, p.35, Vol.3, B.3.2.5 Conc. of a.s in material used, p.39, Vol.1, 1.5.3.3 p.12 Vol.1, LoEP, p.53, Vol. 1, 3.1 Background information, p.91	EFSA: the expression of the active substance used in a.e. might be correct in the practice, however theoretically it may contain any impurities of the technical which have the COOH group. We think the use of picloram would be more appropriate, as the name defines the acid.	
(10)	Vol. 1, LoEP, FAO specification, p.50	EFSA: to avoid further misinterpretation probably it would be helpful to mention that the minimum purity of the FAO specification is on dry weigh basis	
(11)	Vol. 1, LoEP, Boiling point, p.51, Vol.3 B.2.1.2 p.8	EFSA: probably would be better to state that is decomposing at a given temperature	
(12)	Vol. 1, LoEP, Flammability, p.52	EFSA: not highly flammable	
(13)	Vol.3, B.2.2.18 Persistent foam, p.24	EFSA: the foam after 1 minute should be reported	
(14)	Vol. 3, B.5.1.2. Analytical method for impurities, p.50,	EFSA: the method for relevant impurity is not confidential	

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section 1 - Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis (B.1-B.5)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(15)	Vol. 1, LoEP Monitoring methods for soil, p.50,	EFSA: the analytes should be indicated, as the GC-MS method is measuring picloram, while the LC/MS/MS the metabolite XDE-750	
(16)	Vol. 1, LoEP Monitoring methods for water, p.50,	EFSA: the analytes should be indicated, as the GC-MS method is measuring picloram, while the LC/MS/MS the metabolite XDE-750	
(17)	Vol. 3, B.5.2, method 2 (GRM 00.19) plants, p.52, B.5.3.1 method 1 (GRM 00.18) soil, p.53, B.5.3.2 method 1 (GRM 00.17) water, p. 53	EFSA: Is there any information available in the residue methods about the assignment of the fragment-ions used for quantitation and confirmation, to be able to judge the acceptability of the number of fragment-ions used?	

section 2 - Mammalian toxicology (B.6)

20. 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. 1 and Vol.4, Technical specification and toxicological batches	EFSA: RMS could provide a comparison table (purity and impurities) between the technical specification and the toxicological batches (using the same unit to express the content, i.e. %(wet weight basis) or % (dry basis) or g/kg (wet weight basis) or g/kg (dry basis) to ease the comparison).	
(2)	Vol. 1, Active substance Vol. 3, B.6, Toxicological tests	EFSA: The representative technical material (see section 1) is picloram acid. The formulation contains the monoethanolamine salt of picloram. It should be confirmed that this has been adequately addressed in the toxicological studies (no observed adverse effect levels should also be given in picloram acid equivalents). As far as possible for all the toxicological studies, it should be stated which compound/salt has been used and what was the purity. Furthermore, the bridging approach used for the different salts should be discussed in a meeting of experts, taking into account the EPA evaluation (results mentioned in Vol.3 p.92).	

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section 2 - 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
(3)	Vol.3, B.6.3.1, Oral 13-week study in rats, p.78	EFSA: Considering the histopathological findings described in the table B.6.11, the NOAEL might be 150 instead of 300 mg/kg bw/day (at least for the females). Further details on the histopathological observations in the liver might be helpful to conclude on the NOAEL.	
(4)	Vol.3, B.6.5.3, Summary of chronic toxicity, p.105-106	EFSA: According to Reuber, 1981(*), neoplasms at all sites, as well as malignant neoplasms, were increased in both low- and high-dose picloram-treated male and female rats. The malignant neoplasms were both carcinomas and sarcomas. This should be further considered in the evaluation of the carcinogenic properties of picloram.	(*) Carcinogenicity of picloram, by Reuber Melvin Dwaine, Journal of Toxicology and Environmental Health, 7:207-222, 1981 → the rat study evaluated in this article is presumed to be one of the NTP studies referred to in the DAR Vol.3, B.6, p.106.
(5)	Vol. 3, B.6.6.2. Developmental toxicity in the rat, p.110	EFSA: Foetal findings are observed in both rat teratogenicity studies (at 430 and 560 mg/kg bw/d), in presence of a low maternal toxicity (430 was the maternal NOAEL in the first study and 560 was the maternal LOAEL in the second one with reduced BWG and salivation). These findings might be considered relevant for the derivation of the developmental NOAEL.	

section 2 - 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
(6)	Vol. 3, B.6.6.3 Developmental toxicity in the rabbit (with TIPA salt), p.116	EFSA: In the second part of the study (Table B.6.30, p.120), the foetal findings observed at high dose might be taken into account for the derivation of developmental NOAEL of 300 mg/kg bw/day in the rabbit studies.	
(7)	Vol. 3, B.6.10 Summary of mammalian toxicology, p.127, Assessment of the impurity hexachlorobenzene (HCB)	EFSA: We agree that HCB is a toxicologically relevant impurity in the technical specification (see Vol.4). Since a level of 0.2 g/kg has been tested in some of the main tox studies, the proposed level of 0.05 g/kg in the technical specification seems to be covered.	
(8)	Vol. 3, B.6.12.2. Dermal absorption, p.137, in vivo study with rats	EFSA: Several weaknesses are present in this study: a low recovery has been obtained with the concentrate (~85%), a 500-fold dilution has been tested whereas the highest dilution is ~1100-fold. Therefore it could be considered that a part of the amount located in the skin should be included as being absorbed. Has any tape stripping of the skin been performed during this study ?	
(9)	Vol. 3, B.6.14.1. Operator exposure, p.140	EFSA: It should be noted that since the application rate is only 0.35L of formulated product by hectare, the use of 1L pack might not be excluded as a worst-case approach.	

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section 3: Residues (B.7)

21. Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	Vol.3, B.7.1.3 Rotational crop metabolism and B.7.1. Summary assessment	EFSA: It is not clear how the overdosing factor of 285 N was calculated. The application rate in the study was 0.583 kg ai/ha while the notified use is 0.02345 kg ai/ha. Not considering interception the overdosing factor is 25 N. Even if interception were considered (40% at GS 14) this would not result in an overdosing factor of 285 N. Clarification is necessary, since at N rate residues in food and feed possibly exceed the established trigger values. Re-evaluation of rotational crops residues is required.	
	Vol.3, B.7.1. Summary assessment and B.7.3 Residue definition	EFSA: It has been elaborated by the RMS that in plant material picloram is quickly conjugated but also easily released from conjugates after hydrolysis. The presence of significant amounts of conjugated picloram in plants was demonstrated in both the primary and rotational crop metabolism studies. However, only (free) picloram was proposed as the residue definition for oilseeds and cereals. For risk assessment purposes it should be considered whether conjugated picloram has to be included in the residue definition, taking also the residue picture in rotational crops into account.	

section 3: Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	Vol.3, B.7.2.2 Goat metabolism	EFSA: For future reference, to enable accurate comparison with the estimated livestock burden the administered dose in the study should be specified and expressed on a dry matter basis or mg/kg bw basis, respectively. If expressed on an 'as received' basis, the composition of the diet/ dry matter content of the diet used in the study needs to be reported for further conclusions.	
	Vol.3, B.7.2.2 Goat metabolism	EFSA: For future reference, can the impurities of the active substance that showed the same chromatographic behaviour as the non-polar components in the goat studies be named? The increased ratio of impurities to picloram in the fat residue (47:45) could be an indication for preferential accumulation of those impurities in fatty matrices.	
	Vol.3, B.7.6.1 Residue trials	EFSA: In most of the submitted radiolabel studies a hydrolysis step had already been included in the extraction procedure to determine free and conjugated picloram. In the field studies method GRM00.19 was used. Is the extraction procedure in this method suitable to cover also picloram in conjugated form?	
	Vol.3, B.7.7 Storage stability	EFSA: It is noted that the storage period studied is shorted than the time that samples from the residue trials were stored for. Acceptability should be agreed by MS' experts.	

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section 4: Environmental fate and behaviour (B.8)

22. Environmental fate and behaviour (B.8)

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.8.1.1, Route and rate of degradation, Route study a), Knowles, S., Draisey, R., 2001	EFSA: the sampling times of the soils indicated in the text and in the tables (B.8.2 and B.8.3) are slightly different. RMS please check the time of soil sampling and whether the correct days were used in the kinetic calculations.	
(2)	Vol. 3, B.8.1.2, Route and rate of degradation Rate study a) and c), Knowles, S., Draisey, R., 2001; Knowles, 2004a and Cook, W.L., Buehrer, J.T., 1999	EFSA: If using the values in the relevant tables in the Walker equation (and temp. factor of 1.483 in the study c) from 20°C to 25°C) the normalised DT_{50} values would be slightly different. In the case of study c) all the DT_{50} values would be longer than the reported values.	
(3)	Vol. 3, B.8.1.2, Route and rate of degradation Rate study b), Knowles, S., Swales, S.A., 2002 Page 215, 4th paragraph & Tables B.8.12 and B.8.14	EFSA: The largest unknown compound is increasing at the study end (at least in 0-30 cm layer and might be also in 60-100 cm layer) reaching 5.7%AR on day 120. The argumentation supporting that these signals were artefacts is not satisfying (in general the paragraph is not clear). All peaks with radioactivity should come from the parent compound. Could RMS please further clarify the method of detection of this false fluorescence (luminescence?/UV absorption?)? Moreover is it correct that the amounts of Total unknowns are less than the Largest unknown in some cases?	

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section 4: Environmental fate and behaviour (B.8)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(4)	Vol. 3, B.8.1.2, Route and rate of degradation Rate study c), Cook, W.L., Buehrer, J.T., 1999 Page 281 bottom and Table B.8.22	EFSA: The application rates used in the study as indicated are not equal with 134, 235, 504, 773 and 1052 g/ha (assuming even distribution in the top 5 cm layer of soil), they are much less, however still higher than the expected soil concentration resulted by the application of picloram according to the GAP. RMS pls check what were the application rates in the study (and compare with application rate according to the GAP/PECsoil) or clarify this calculation and that still only the DT50s from the experiments with the smallest dose should be used in the exposure calculations.	
(5)	Vol. 3, B.8.1.2, Route and rate of degradation Rate study c), Cook, W.L., Buehrer, J.T., 1999	EFSA: RMS please add data if there were information about microbiological activity of the soils during the study. Please give more argumentations which support the exclusion of the DT_{50} values calculated from the higher dose experiments. Moreover it would be nice to see the correlation between the dose and the degradation (please see also EFSA comment 4 above). Note: The inclusion/exclusion of the results of the study by McCall, P.J., Jeffries, T.K., 1978 (route b), rate d)) might depend on the acceptability of the argumentation as (in the DAR) these results are excluded for the same reason.	

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section 4: Environmental fate and behaviour (B.8)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(6)	Vol. 3, B.8.1.5, Summary and assessment	EFSA: The DT50 values from the Rate study b), Knowles, S., Swales, S.A., 2002 were reported (calculated by the RMS) in Annex B (not in the LoEP), but not used further in the exposure assessment without any argumentation. RMS please clarify why the DT50 values are not used further from this study.	
(7)	Vol. 3, B.8.1.3, Photolysis in soil Fontaine, D.D., Woodburn, K. B., 1986, & Vol. 1	EFSA: The light source used in the soil photolysis study was not accepted by the Rapporteur, however the results (no photodegradation) appear in the Volume 1 (page 29 and LoEP) hence the opinion of the RMS about the acceptability of any result or the study itself is not clear. In Level 4 of Volume 1 (under the point 4.2.8) RMS suggests to address the requirement of proper soil photolysis at MS level, however soil photolysis is an Annex II requirement and the potential metabolism via soil photolysis should be clarified for Annex I listing.	
(8)	Vol. 3, B.8.1. 3, Photolysis in soil Fontaine, D.D., Woodburn, K. B., 1986, Table B.8.26	EFSA: The recovery of this study can not be reproduced by the values reported in this Table. RMS please clarify this. Moreover it is not clear whether the values referring to picloram are the percentaged values of the organic extracts (i.e. 99.7 or 100% of the organic extracts were picloram).	

section 4: Environmental fate and behaviour (B.8)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(9)	Vol. 3, B.8.1.3, Field studies b), Knowles, S., Brice, A., 2003 Table B.8.30	EFSA: To use the half of the LOQ and the 20% of the LOQ for all the not detected (ND) values are not in line with the FOCUS degradation kinetic guidance (FOCUS 2005). RMS please clarify what were the actual measured residue values at least for cases where they were above the LOD and please recalculate the DT_{50}/DT_{90} values as recommended by FOCUS Kinetic guideline if necessary. The note below the table marked with '*' is not clear.	
(10)	Vol. 3, B.8.1.3, Field studies c), Knowles, S., Schnöder, F., 2003a Page 235 & Table B.8.32	EFSA: Could RMS please clarify what exactly mean that for calculating the total extractable radioactivity (TRR) similar (to the top layer) extractability was assumed? What were the exact values in this calculation? The value of 1.54% AR means that this amount of radioactivity (assumed extractable + non extractable) was measured in the soil layer below 10 cm immediately after the application? No changes in the values referring to the 0-10 and 0-20 cm up to 7 days in the Table B.8.32.	

section 4: Environmental fate and behaviour (B.8)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(11)	Vol. 3, B.8.1.3, Field studies c), Knowles, S., Schnöder, F., 2003a Table B.8.33	EFSA: Could RMS please clarify what the column 'Total incl. procedural recovery' mean and how procedural recovery was determined. If the procedural recovery was around 100% at each day why the values for picloram were not accepted for kinetic analysis? Is it correct that at two cases there is more picloram, than the total AR (2nd column incl. procedural recovery)? All the values in the table refer to %AR? In general it is not easy to understand this table and the study description.	
(12)	Vol. 3, B.8.1.3, Field studies c), Knowles, S., Schnöder, F., 2003a	EFSA: RMS please check the full study description as some data is not correct or not clear comparing with the original study report (e.g. description of the soil, whether unextracted residue is 0.59 or 0.39 %AR as indicated in the Summary and Conclusion of the report).	
(13)	Vol. 3, B.8.2.4, Summary and assessment	EFSA: Please add argumentation why the results from the study by Knowles, S., Swales, SA., 2002 were not used further in the exposure assessment.	
(14)	Vol. 3, B.8.2.4, Summary and assessment & PECgw and PECsw	EFSA: As no Freundlich isotherm was established for 1/n 1 should have been used instead of 0.9 in the PEC calculations.	
(15)	Vol. 3, B.8.2.3, Lysimeter studies or field leaching studies	EFSA: RMS please clarify whether there was or not another lysimeter study with picloram on 'HAN' soils (see B.8.1.2 b), and B.8.2.1 b)). If this lysimeter had been performed with picloram could RMS pls. give details about the study?	

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section 4: Environmental fate and behaviour (B.8)

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(16)	Vol. 3, B.8.4.4, Water/sediment studies Table B.8.58	EFSA: RMS please confirm that from the French system duplicate samples were taken on day 31 and single sample on day 21 and in the Italian system the opposite. Please see also EFSA comment (21) on the LoEP and consider the possible effects of these on the kinetic evaluation.	
(17)	Vol. 3, B.8.6, Predicted environmental concentrations in surface water and groundwater (PECsw and PECgw)	EFSA: In the PECsw calculations for the metabolites the maximum observed values were used. As the maximum amounts were observed at the study end when still there were significant amount of parent (>50%), it cannot be excluded that the maximum occurred of these metabolites in w/s systems would be more (theoretically about twice that assumed in current calculations).	
(18)	Vol. 3, B.8.6, Predicted environmental concentrations in surface water and groundwater (PECsw and PECgw)	EFSA: Please clarify whether are there any scientific reason/fact/argumentation to support that the 5,6-dichloro analogue is expected to have comparable adsorption properties to the 3,6-dichloro analogue.	
(19)	Vol. 3, B.8.6, Predicted environmental concentrations in surface water and groundwater (PECsw and PECgw)	EFSA: It is noted that the 3,6-dichloro analogue is aminopyralid and that the adsorption study for aminopyralid is not evaluated and summarised in this DAR for picloram. As the peer review of the DAR for aminopyralid has not been completed and picloram may progress through the peer review program in advance of aminopyralid an assessment of the available adsorption study needs to be presented.	

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section 4: Environmental fate and behaviour (B.8)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(20)	Vol. 3, B.8.6, Predicted environmental concentrations in surface water and groundwater (PECsw and PECgw)	EFSA: The application windows used in the FOCUS Step 3 PECsw calculations (15 Feb.-15 March) and the actual appl. dates for winter oilseed rape (February for all scenario) seems to be too early for spring application (and of course too late for autumn appl.). Could RMS please clarify whether the application time is restricted to spring application (in the GAP table only BBCH 14-31 is mentioned)?	
(21)	List of End Points	EFSA: • Soil Rate box: it should be indicated that the soil classification based on UK/BBA classification or US classification, (w) means that pH was measured in water and where there is no indication what was the media to measure the pH. • Adsorption / desorption data for aminopyralid (3,6-dichloro analogue) are not included but have been used to calculate PECsw • Field dissipation box: pH of the German study is 6.6 while in the DAR is 6.0. The media in which the pH values were measured should be indicated in the LoEP as there were measurements in different medias. • lysimeter box: please indicate clearly that only one application was performed in the first year • PECgw box: please remove data referring to	

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section 4: Environmental fate and behaviour (B.8)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		the lysimeter from the box of PECgw • PECsw box: when calculating average from 2 replicates, values <LOQ should be considered as equal with LOQ (here 1.1%) rather than 0. This would result 5.2% 3,6-dichloro as max in sediment and 1.1% 5,6-dichloro analogue as max in water (instead of 4.6% and 0.6%) or take the actual value from the repetition where it was measured as at least the values of 9.2% and <LOQ are quite far from each other (and do not look like consistent between the two systems). • Quantum yield of direct phototransformation in air: please clarify were the included value come from as no indication for that value in Annex B.	
(22)	Vol. 3, B.8.11 References relied on & Vol. 2	EFSA: All references regarded as not relied on should be removed from the lists. References for 'Plant Protection Product' should contain only those studies which particularly refer to the PPP and not the a.i. (e.g. PEC calculations).	

section 5: Ecotoxicology (B.9)

23. Ecotoxicology (B.9)

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.9.1.1.1. acute oral toxicity to birds, Beavers 1986a study, pag 288	EFSA: RMS could provide an explanation on the conversion factor use to convert the endpoint from picloram potassium salt to picloram acid equivalent	
(2)	Vol. 3 B.9.1.2.1. acute oral toxicity to birds, Beavers 1986b study, pag 290	EFSA: RMS could provide an explanation on the conversion factor use to convert the endpoint from picloram potassium salt to picloram acid equivalent. The raw data should be reported for causes of transparency (i.e tables with the body weight and food consumption during the test).	
(3)	Vol. 3 B.9.2.1.1. acute toxicity to aquatic organisms, Desjardins 2001 study, pag 302	EFSA: The raw data should be reported (i.e. tables with the observations).	
(4)	Vol. 3 B.9.2.1.1. acute toxicity to aquatic organisms, Hughes 1990 study, pag 304	EFSA: RMS could provide a explanation on the conversion factor use to convert the endpoint from picloram potassium salt to picloram acid equivalent	