Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at Community level of

Flufenoxuron

ECHA/RAC/ CLH-O-0000001741-79-01/A2

Adopted

10 June 2011

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

[ECHA has compiled the comments received via internet that refer to several hazard classes and entered them under each of the relevant categories/headings as comprehensive as possible. Please, note, that some of the comments might occur under several headings when splitting the given information is not reasonable.]

Substance name: Flufenoxuron
CAS number: 101463-69-8
EC number: 417-680-3

General comments

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
20/04/2010	Japan / K Tomeba / Individual	ECHA: comments were not included		
06/05/2010	Germany / Jan Averbeck / Member State	The German CA recommends RAC to consider the C&L discussion on Flufenoxuron in EFSA. In beginning of 2010 the discussion about C&L was reopened because new study results (not included in CLH-Dossier) were submitted to EFSA. In our point of view it would be useful to involve the "co-ordinator for the maintenance of close, direct and continuing contacts between the Agencies" into the CLH-process. Page 4 It was noted that the proposal for C&L of Flufenoxuron as a biocide according to Directive 98/8/EEC were different from those that were recently made in the	FR: The Biocide and Pesticide dossiers were evaluated in parallel in France. But this CLH dossier takes into account all studies from both dossiers and aims to establish a final harmonized classification for flufenoxuron. In this purpose, the new genotoxicity studies have been included in the revision of the CLH report. However, we consider that it doesn't bring sufficient evidence to classify R40 for carcinogenicity.	I rely on the opinion expressed by France which has prepared both documents.

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		evaluation as a pesticide according to Directive 91/414/EEC (resubmission proposal from France, Additional Report). In the latter document, the same RMS proposed R64 and, in addition to the current CLH dossier, R40 but no other classifications for health effects. Harmonisation is considered to be necessary. The proven strong bioaccumulative potential of Flufenoxuron is a crucial point for understanding of the toxic effects resulting in a need for classification and labelling, in particular with regard to reproduction. Toxicikinetics of Flufenoxuron were characterized by delayed elimination and accumulation mainly in fat but also in other tissues such as blood, skin, ovaries, liver, or bone marrow. 7 days after single oral administration of 3.5 mg/kg bw to rats, residues in fat, carcass (including body fat), and skin, accounted for 27%, 37-45%, or 12-19% of the applied dose. Repeated administration (3.5 mg/kg bw/day over 4 weeks) resulted in concentration of 144 ppm in fat and 33 ppm in bone marrow. Half-lives ranged from 28 days in fat and carcass to 48 days in the liver. When rats were fed a diet containing 500 ppm Flufenoxuron for 100 days, fat residues amounted to 230 ppm.		

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11/05/2010	UK / Member State	Page 1: Please would the RMS check if the date should be February 2010 instead of February 2009. Pages 4/5: There is a discrepancy between the purity stated on page 4 (≥ 950g/kg) and the typical concentration/concentration range on page 5 (≥ 96%) that should be corrected. We do not support the proposals to classify for Repr. Cat3; R63, R64, Xn; R48/22 (Repr. 2 – H361d, Lact. – H362, STOT Rep. 2 – H3737).	FR: The date has been corrected.. FR: The correct values are 950 g/kg for the purity and ≥ 95% for the concentration range. These items will be corrected. FR: noted.	Remarks are noted Remarks are noted
12/05/2010	Belgium / Frederic Denauw / Member State	Please find the belgian comments Preliminary remark BE: It is of note that the proposal for C&L was introduced although the discussion in the wg PPP was not finalised yet. In 02/2010, several new mamtox studies have been submitted to RMS FR (accelerated procedure). These included a new sensitisation assay, an Ames-test, an in-vitro gene mutation assay, an in-vivo rat bone marrow clastogenicity study on the substance itself, and several genotoxicity studies on Reg No. 241208 (metabolite of Flufenoxuron). In addition, the RMS of the wg PPP proposed an additional classification	FR: The sensitisation assay was already included in the report but the new genotoxicity studies have been added. The new Ames test and the *in vitro* gene mutation assay in V79 are negative. In the *in vivo* chromosome aberration assay, one multiple aberration and two exchanges were observed in the 48-hour (top dose) group only and the overall cells remained unaltered when compared with solvent controls. Therefore, despite the fact that these findings are considered as extremely rare, the toxicological significance of the low incidence of these aberrations is questionable.	Thanks for advice. No classification is proposed for mutagenicity and carcinogenicity of flufenoxuron

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		(Carc. Cat. 3, R40), on the basis of the observed increase of splenic haemangiosarcoma in the female mouse. The RMS wg PPP considered the observation relevant, as in addition, there was some reservation about the negative outcome in the new in-vivo clastogenicity assay. Therefore, it would be necessary to include the new information in the present CLH report, to allow a transparent evaluation of this substance.	In the carcinogenicity studies, no increase in tumours was observed in rats. In mice, the incidence of hepatocellular carcinoma observed in males at the 2 lowest doses was associated with unusually low incidence of these tumors in the control. At the highest dose (7,780 mg/kg bw/day), this effect was associated with a toxic context. Increased incidence of vascular tumours was also observed in female mice and was probably due to the exaggerated dose, higher than the maximum tolerated dose (7,780 mg/kg bw/day). Therefore these findings observed at a very high dose in a toxic context are considered insufficient to warrant a classification R40. Discussion has been added to clarify our point of view.	
14/05/2010	Portugal / Member State	Considering the present proposal, we agree to establish a harmonised classification and labelling for FLUFENOXURON. The proposed classification and labelling fulfills the criteria established both in CLP Regulation and 67/548/EEC Directive (health and environment). Therefore, we support this proposal.	FR: Thank you.	Thank you

Carcinogenicity

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
06/05/2010	Germany / Jan Averbeck / Member State	Page 32-34 We agree with the conclusion of the RMS not to classify Flufenoxuron for carcinogenicity. The respective proposal as recently made in the evaluation of this substance as a pesticide under Directive 91/414/EEC was based on suspected clastogenicity. This approach is certainly not appropriate, because the occurrence of chromosome aberrations in rats in vivo should be further investigated before a final assessment can be made. "Precautionary" allocation of the risk phrase R40 cannot replace proper investigations on mutagenicity. If such a clastogenic potential would be confirmed, R68 was more appropriate.	FR: Thank you. The new genotoxicity studies have been included. In the *in vivo* chromosome aberration assay, one multiple aberration and two exchanges were observed in the 48-hour (top dose) group only and the overall cells remained unaltered when compared with solvent controls. Therefore, despite the fact that these findings are considered as extremely rare, the toxicological significance of the low incidence of these aberrations is questionable. The lack of any genotoxic effects following *in vivo* exposure to flufenoxuron is confirmed in a mouse bone marrow micronucleus assay and in an *in vivo/in vitro* UDS test, in rat liver cells. No classification for this endpoint is warranted. In the carcinogenicity studies, no increase in tumours was observed in rats. In mice, the incidence of hepatocellular carcinoma observed in males at the 2 lowest doses was associated with unusually low incidence of these tumors in the control. At the highest dose (7,780 mg/kg bw/day), this effect was associated with a toxic context. Increased	Thank you. No classification is proposed for this endpoint.

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
			incidence of vascular tumors was also observed in female mice and was probably due to the exaggerated dose, higher than the maximum tolerated dose (7,780 mg/kg bw/day). Therefore these findings observed at a very high dose in a toxic context are considered insufficient to warrant a classification R40. Discussion has been added to clarify our point of view.	
11/05/2010	UK / Member State	Page 32/33. The UK supports the position not to classify for carcinogenicity. However, we would like to see more information in the table of the incidences of hepatocellular and vascular tumours seen in each group, to allow a more thorough evaluation of the evidence (first mouse study, Esdaile 1990, 1991; Berry, 1992). For example, one of the reasons to dismiss the hepatocellular carcinomas in male mice in this study is the absence of a dose-response relationship, but this information was not shown.	FR: Thank you. A table of the incidences of hepatocellular tumours and hemangiosarcoma in the spleen has been added.	Thank you. No classification is proposed for this endpoint
12/05/2010	Belgium / Frederic Denauw / Member State	Carcinogenicity (i) Hepatocellular carcinoma frequency significantly higher in all treated groups of male mice (38***, 30**, 30** %, at 500, 5000, 50000 ppm), but remained within historical control data (HCD, which was higher than study ctrl incidence of 6%). Whereas this effect was	FR: We agree that the effects observed (hepatocellular carcinoma and splenic hemangiosarcoma) are not sufficient to lead to a classification for carcinogenicity.	Thank you. No classification is proposed for this endpoint

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		not dose-related, and the study ctrl unusually low, the relationship with treatment at the two lowest doses remains questionable. At the top-dose, the effect is not considered fortuitous, as liver is the target organ, and significant organ damage was demonstrated (cell necrosis). (ii) Splenic haemangiosarcoma in high-dose females (0, 2, 2, 14** %, at 500, 5000, 50000 ppm) were statistically higher than in controls, largely contributing to a higher incidence of vascular tumours in this high dose treated group (haemangiomas, haemangiosarcomas combined at any location: 22% high-dose females). The notifier provided a position on the splenic haemangiosarcoma: "Similar changes have been reported for other chemicals (aniline, p-nitroaniline, and p-chloronitrobenzene being mentioned) which also cause blood changes similar to those seen with flufenoxuron. These tumours are considered unlikely to be of genotoxic origin, but more likely to be related to definable threshold-related processes". It was noted that the effect was only observed at a excessively high toxic dose (50000 ppm= 7780 mkd), and was not observed in a second study at 10000 ppm= 1890 mkd). In conclusion, the effect is probably substance-related but		

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		considered insufficient to warrant a classification for carcinogenicity.		

Mutagenicity

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
06/05/2010	Germany / Jan Averbeck / Member State	Page 31 A more recent in vivo study [Honarvar, N. (2007): Chromosome aberration assay in bone marrow cells of the rat with Flufenoxuron. RCC, RC Cytotest Cell Research GmbH, Rossdorf, Germany, Unpublished report no. 2007/1050086] was submitted for pesticide evaluation (see Additional Report of the RMS France, February, 2010) and was found indicative of a clastogenic potential. For evaluation of Flufenoxuron as a biocide, this report was obviously not made available. This evidence should be clarified before a final decision on C&L is taken.	FR: The new genotoxicity studies have been added to consider in the CLH dossier all studies from the Biocide and the Pesticide dossiers. In the *in vivo* chromosome aberration assay, one multiple aberration and two exchanges were observed in the 48-hour (top dose) group only and the overall cells remained unaltered when compared with solvent controls. Therefore, despite the fact that these findings are considered as extremely rare, the toxicological significance of the low incidence of these aberrations is questionable. The lack of any genotoxic effects following *in vivo* exposure to flufenoxuron is confirmed in a mouse bone marrow micronucleus assay and in an *in vivo/in vitro* UDS test, in rat liver cells. Hence, flufenoxuron is considered not genotoxic and no classification for this endpoint is warranted.	Thank you. No classification is proposed for this endpoint
11/05/2010	UK / Member State	Page 32. The UK supports the position not to classify for mutagenicity.	FR: Thank you.	Thank you. No classification is proposed for this endpoint
12/05/2010	Belgium / Frederic Denauw / Member	Genotoxicity Although RMS has reservations upon the	FR: Agree. The new genotoxicity studies have been added.	Thank you. No classification is proposed for this endpoint

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	State	acceptability of some genotoxicity studies (top-dose too low), BE considers that overall, the studies are acceptable, as valid studies exist in the package. In addition, cytotoxicity was sometimes demonstrated in preliminary cytotoxicity tests but not in the main tests, explaining the choice of the top-dose. In-vitro: not genotoxic, taking into account new studies (2007, not included in the CHL data package); In-vivo: -Rat BM CA assay (Allen, 1986) was conducted at 4000 mk, inducing clear clinical signs, but considered inconclusive by RMS because of no data on MI, polyploidy counts and 50 cells i.o. 100 cells/animal scored. Despite these minor deficiencies, BE considers the study sufficiently acceptable to support the conclusion of non-clastogenicity. -Mouse MN assay (Nishitomi, 1993) was conducted at 2´500, 2´1000 and 2´2000 mk, inducing no clinical signs. However, given the toxicokinetic data, where adequate absorption was demonstrated, systemic exposure was anticipated, and therefore BE considers the study sufficiently acceptable to support the conclusion of non-clastogenicity (the limit dose is 2 g/kg/day for treatment periods of 14 days or less, and considered acceptable even if there is no evidence of toxicity).		

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		-Rat BM CA assay (Honarvar, 2007) was conducted at 500, 1000 and 2000 mk, where clinical signs were observed. No CA was observed, except at 2000 mk (at 48h but not at 24h sacrifice), where one multiple aberration and two exchanges were observed. However, the overall % aberrant cells remained unaltered when compared with solvent controls. Therefore, the genotoxicological significance of the low incidence of this (extremely rare) aberration remains questionable. Globally, BE considers that Flufenoxuron is devoid of genotoxicological potential, and classification (Xn,R68 or Muta. 2, H341 is not warranted).		

Toxicity to reproduction

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
06/05/2010	Germany / Jan Averbeck / Member State	Page 34- 43 We agree with the proposal to allocate Repr. 2 H361d and Lact. H362 although the first proposal was not made in the evaluation according Directive 91/414/EEC. Nevertheless we think there is a need for discussion about the proposal to classify Flufenoxuron as developmental toxicant and for effects on or via lactation. Particularly the fact that the observed effects in the 2-generation study are	FR: Further to the feedbacks received in the process of the Pesticide and Biocide dossiers of flufenoxuron, the overall dataset has been reconsidered between the French agencies in charge of these dossiers. The effects seen in the two-generation study were not reproduced when exposure of pups was limited to either: - gestation and lactation without long pre-gestational exposure of	Thank you. The opinion of France is supported and classification Lact. H362 is proposed

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		supposed to serve as justification for both proposed endpoints for classification (Repr. Cat 2 H361d and Lact. H362) deserve closer attention and discussion. The increase in total litter loss observed in the 2-generation study is unincisive as the reduction of mean litter size in the F2a generation amounts to 2 pups. Neither the cross-fostering study nor the dietary investigative study affects the pup mortality or the lactation indices. On the basis of the available data the connection of in utero exposure and the occurrence of increased pup mortality which would be crucial for classification can not be reconstructed. Further information and detailed discussion are needed.	dams (exposure from GD3 to weaning in James and Jones, 1992) or - gestation with a maternal exposure from 10-week prior to mating until parturition (treated pups from treated dams reared by control dams in Masters, 1996) or - lactation with a maternal exposure from 10-week prior to mating until parturition (control pups from control dams reared by dams treated from 10 weeks prior to mating until parturition in Masters, 1996). But because exposure of the treated dams was stopped at parturition and the level of flufenoxuron was shown to decrease rapidly in milk during lactation, exposure of pups during lactation is considered as limited and the results from this group have to be used with caution. Besides, the presence of flufenoxuron in the maternal milk (analysed in the cross-fostering study), the fact that some of the dead pups showed absent or minimal stomach content (2-generation study) and the dams' difficulties to lactate properly (CKA test) contribute to point to an effect via lactation. As pointed out in several comments, toxicokinetic of flufenoxuron is important to understand its	

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
			toxicological profile. Its ability to accumulate in fat may explain that a long pre-lactation exposure of dams to flufenoxuron is necessary to accumulate and lead to adverse effect via lactation and the apparent discrepancy between the two-generation study and the studies with exposure by segment. The fact that effects on pups occur not immediately after birth also point out to an effect due to lactation. Although it cannot be excluded that the pup mortality and decreased pup body weight observed in the 2 generation study could also be caused by a cumulative exposure during gestation and lactation, it is more plausible that these effects are due to effect on lactation (transfer of flufenoxuron though the milk and/or perturbation of the lactation). Furthermore, no evidence of a direct effect of flufenoxuron *in utero* is available as no adverse effect on foetus was observed in teratogenicity studies and after exposure to flufenoxuron from day 3 of gestation to weaning or from 10 weeks prior mating until parturition. Therefore it is considered that the evidence of an *in utero* effect is not sufficient to support a classification for developmental toxicity. The proposition R63 has therefore been deleted. R64 is maintained.	

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			More details have been added in the CLH report to propose hypothesis on the possible mechanism explaining the reduction/losses in pup weight and viability.	
11/05/2010	UK / Member State	Fertility Page 43. We agree with no classification for fertility effects. Developmental toxicity P 39. It is reported that, in the two-generation study, the dead pups frequently showed absent or minimal stomach contents. Are any further details available, such as how many animals and which groups they were in? P 42. A suggested adverse effect of flufenoxuron is perturbation of the mammary development and lactation process. Is there any evidence to support this conclusion, for example histopathological investigations of the mammary gland? P 43. Summary and discussion. The dossier proposes classifications for Repr. Cat. 3; R63 (based on decreased pup survival and development) and R64 (based on an adverse effect on the quantity of milk produced, which was purported to be a result of a negative	FR: Thank you. The number of pups with minimal stomach contents were as following: F1a: 2 female at 190 ppm F1b: 1 female at 190 ppm F2a: 1 male at 190 ppm and 1 male at 10,000 ppm F2b: 2 males and 1 female at 710 ppm Mammary gland was only weighted (no effect) in the 2-generation study. No histopathological examination was performed. As explained above the proposal R63 has been deleted. However, it is not considered that the effects observed in pups can be attributed to maternal toxicity. Indeed, the reduction of body weight in females was observed for the pre-mating period prior to the first mating	Thank you for support The proposal of France to classify Lact. H362 (CLP) and R64 (DSD) is supported in view of the data presented in BD

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		effect on mammary gland development, with a consequent decrease in pup survival and development during lactation). The evidence for a developmental effect during lactation is limited. The effects on pup survival noted in the two-generation study were generally small, occurred at high doses and were probably associated with maternal toxicity (decreases in weight gain, weight loss, organ weight changes; also, information from the repeated-dose studies indicates that some anaemia would be expected in the dams of the higher dose groups). The evidence for an effect on mammary gland development is likewise sparse: the cross-fostering study did not investigate lactation-only effects; the embryotoxicity study did not give consistent results across all females of the high-dose group and was, besides, unreliable; in no study was milk production measured or effects of test substance on mammary gland development determined histologically. Therefore, the available information is not adequate to support classification with R63 and R64 / Repr. 2 – H361d and CLP Lact – H362	but the overall body weight gains were comparable for all groups during the two gestation periods. During lactation periods, body weight gains were similar for F0 females but were statistically significantly decreased in F1b female group at the top dose during the first lactation period (decrease up to 5%). Concerning organ weight changes, they were not associated with an increase of histopathological findings. Two possible mechanisms were proposed to explain the reduction/losses in pup weight and viability (Christian, 2007): - Inhibition of maternal lactation and reduced milk fat content as the result of reduced triglyceride levels in the dams, - Reduced triglyceride levels in the pups secondary to reduced maternal milk quality and direct exposure to flufenoxuron via maternal milk and, later, via maternal diet. These hypothesis were based on the distribution of flufenoxuron in the body (high affinity for fat; presence of flufenoxuron in the milk of lactating rats) and on the results of the repeated-dose toxicity studies in rats where reduced triglycerides levels were noted. According to the Directive 67/548/EEC	

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			criteria for R64 are the following: *R64 would normally be assigned on the basis of:* *- toxicokinetic studies that would indicate the likelihood that the substance would be present in potentially toxic levels in breast milk; and /or* → In the cross-fostering study (Masters, 1996), flufenoxuron was detected in the milk of lactating rats. Flufenoxuron has a low acute toxicity in adult animals. However, the toxicity in young animals is not known and it is not considered possible to establish what potentially toxic levels in breast milk are. In the 2 generation study, decreases of viability and lower pup body weights were observed during lactation and based on the absence of effect with in utero exposure only, these effects are considered as an evidence of the toxic effect of flufenoxuron in milk. *- on the basis of results of one or two generation studies in animals which indicate the presence of adverse effects on the offspring due to transfer in the milk; and/or* → In the 2 generation study, decreases of viability and lower pup body weights were observed during lactation. The cross-fostering study failed to demonstrate that effect was due to an *in utero* exposure only. The preliminary	

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			study failed to demonstrate that effect was due to exposure during gestation and lactation without long pre-gestational exposure of dams. The toxico-kinetic profile of flufenoxuron and the observation of effects linked to lactation (transfer of flufenoxuron though the milk and indications of an inhibition of the lactation) support that the effect is likely to be due to flufenoxuron in milk and that a long pre-exposure of dams to flufenoxuron is necessary to accumulate and lead to adverse effect via lactation. These criteria are respectively similar to point (b) and (c) of the CLP criteria. Therefore we consider that the effects observed in the reproductive studies associated with toxicokinetics data are sufficient to allocate R64. Concerning the R63, it was decided that the evidence was not sufficient enough to support this classification considering that it is more plausible that the pup mortality and decreased pup body weight observed in the 2 generation study are due to effect on lactation (transfer of flufenoxuron though the milk and/or inhibition of the lactation). See also response to Germany on page 10.	
12/05/2010	Sweden / Helena	Reproductive toxicity	FR: The R63 has been deleted considering	The proposal of France to classify Lact.

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
	Kramer / Member State	We agree that the proposed classification for reproductive toxicity, Repr. Cat.3;R63 (CLP Repr. 2– H361d), based on reduced pup survival is justified. We agree that the proposed classification for reproductive toxicity, R64 (CLP Lact.– H362), based on reduced pup survival and their development during lactation is justified. *Transferred from general comments by ECHA.*	that the evidence is not sufficient to support this classification. See also response to Germany on page 10. Thank you.	H362 (CLP) and R64 (DSD) is supported in view of the data presented in BD
12/05/2010	Belgium / Frederic Denauw / Member State	fertility –development –lactation (i) 2G -Over the whole 2-generation study, there were 1, 1, 2, 8 and 13 total litter losses during lactation at 0, 50, 190, 710 and 10000 ppm respectively (significantly higher at the two highest doses) than in controls. -Smaller litter size (up to -26%) and higher cumulative dose-dependent pup loss (up to +1293% of control) were observed at a significant level on d21 pp at the top dose. Pup mortality at 10000 ppm and to a lesser extent at 710 ppm, both in litters totally lost and in litters where dams reared some young to weaning, was associated in many instances with failure to gain weight or actual weight loss in the period prior to death. Deaths at 10000 ppm included a	FR: Agree. The R63 has been deleted considering that the evidence is not sufficient to support this classification. See also response to Germany on page 10.	Thank you for support to classify Lact. - H362 (CLP) and R64 (DSD) in view of the data presented in BD

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		number of pups which were sacrificed in a moribund condition particularly in the F1b generation. Where it was possible to make an assessment, these dead pups frequently showed absent or minimal stomach content. Note: The data were not corroborated in a cross-fostering study (pups from untreated dams reared by treated dams, and vice-versa pups from treated dams reared by untreated dams), however the treatment was different, and the effects observed in the 2G study may be due to accumulation of the substance, and/or feeding of the pups after birth. (ii) Developmental studies - Pregnant rats treated (d8-17) at dose levels of 0, 10 and 1000 mkd by gavage in a screening assay did not result in maternal toxicity. High dose dams (4/14) had difficulties to lactate properly which resulted in the complete loss of 2 litters and increased pup mortality and impaired body weight development in the two other litters. - In the full study (treated d6-16) at 0, 7.9, 100 and 1000 mkd, the total number of live implants was minimally lower at the top-dose than in controls (-2.5%), corresponding to a higher number of early embryonic deaths (+38% relative). An increase of the incidence of heart vessel		

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		branching at the top-dose (variation) was considered irrelevant by the RMS. - Pregnant rabbits treated (d6-18) at 0, 7.7, 100 and 1000 mkd exhibited no adverse effects, but a marginal increase in heart vessel branching variations and delayed ossification, along with slightly reduced mean foetal weight, was observed at top-dose. Conclusion: RMS considered Flufenoxuron not teratogenic. -The increased incidence of variations in the full rat and rabbit studies occurred in the total absence of maternotoxicity. However, as the increase was marginal in the rabbits, and only slightly above HCD in rats (litter incidence study: 22%, HCD: up to 18%; foetal incidence study: 4.9%, HCD: 3.4%), and as these common branching alterations are considered variations rather than abnormalities, RMS position is accepted. -Concerning the effects of the substance on the lactation The effects observed in the 2G study may be the consequence of both a decreased quality of the milk and/or nursery failure, although an effect due to the feeding of the pups at early phases is not excluded. The effects observed in the rat		

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		developmental sighting study indicate clearly a failure of lactation. Overall, the effects would justify a classification R64 - H362. The consequence is pup death at the top-dose, but there are no indications that the effects are caused by an in-utero exposure, although it is not excluded. The small increase (by 2%) of early deaths in the full rat developmental study does not justify the classification as developmental toxicant. It is plausible that the effect on lactation is much more important. Based upon the lipophilicity of the substance and concomitant transfer into the milk, this hypothesis is more plausible.		
12/05/2010	Sweden / Helena Kramer / Member State	5.8.1 Effects on fertility p. 39. "Fifteen control and 5 treated dams reared their offspring until weaning without cross-fostering" The group of 5 treated dams and their offspring is treated during pre-mating, mating, gestation and during the lactation period. Since all results indicate that the adverse effect on pup survival are likely due to exposure both in utero and through milk, one would expect to see this effect in the offspring. If this data is available it would strengthen the argumentation. p.43 5.8.5	FR: The survival of pups assessed by the viability and lactation indices was not affected by treatment in any group and pup body weight development was comparable between all groups (including the group "treated dams/treated pups"). This information has been added in the CLH report. However, it should be noted that exposure of the treated dams was stopped at parturition and the level of flufenoxuron was shown to decrease rapidly in milk during lactation. Exposure of pups during lactation in this group was therefore limited and the results from this group have to be used with caution. Besides the small size of this group (5 dams) limits the interpretation.	The remarks have been utilized and comparison of data with classification criteria was provided in the draft opinion.

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		The argumentation in the summary and discussion section would benefit from a thorough comparison between the classification criteria and the study results.	OK. An argumentation has been added.	
14/05/2010	Spain / Elina Valcarce / Member State	3 Summary and discussion of reproductive toxicity The Spanish CA supports the proposed classification of flufenoxuron as R64 "May cause harm to breastfed babies" under Directive 67/548/EEC and as Lact – H362 under Regulation (EC) 1272/2008. There is clear evidence that the adverse effects observed in the offspring (reduced pup survival) are mainly due to lactational exposure. Besides, the Spanish CA endorses the proposed classification of flufenoxuron as Repr. Cat.3; R63 "Possible risk of harm to the unborn child" under Directive 67/548/EEC and as Repr.2 – H361d under Regulation (EC) 1272/2008. We agree with French CA that the adverse effects in the offspring (pup mortalities) can also be considered to be developmental toxicity as it can not be ruled out that they are induced in part by prenatal exposure. The cross-fostering study indicates that an exposure of pups both in utero and milk is required to produce adverse effect in the offspring. Therefore, we believe that the	FR: Thank you. FR: the R63 will be deleted considering that the evidence is not sufficiently enough to support this classification. See also response to Germany on page 10.	Thank you for support.

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		criteria for developmental toxicity classification is fulfilled.		

Respiratory sensitisation

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
11/05/2010	UK / Member State	The UK supports the position not to classify for respiratory sensitisation.	FR: OK. Thank you.	Thank you

Other effects - Physico-chemical properties

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
06/05/2010	Germany / Jan Averbeck / Member State	Physico-Chemical Properties The evaluation and classification of physico-chemical hazards for the endpoints - Explosivity - Flammability - Oxidising properties is not possible because information on physico-chemical studies (Van Helvoirt J.A.M.W. et al., 1990) is not available in IUCLID dataset.	The IUCLID 5 was not filled because it is not compulsory to complete the robust study summaries for the biocide substances at present. But further information concerning these studies has been added in the CLH report.	No classification is proposed for these endpoints.
11/05/2010	UK / Member State	Page 14: Summary and discussion of acute toxicity. The final statement that 'These data are only submitted to provide a toxicological profile for flufenoxuron' should be removed, since all end-points are evaluated for active substances under Directive 98/8/EC.	FR: Agree. It has been modified.	Thanks for your remark, which has been used.

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		Page 15: Eye irritation. We agree that no classification is needed for eye irritation. However, since there was minimal/slight irritation (score for redness of the conjunctiva 0.33), there should be a brief explanation that this does not meet the EU criteria (result was less than the score of ≥ 2.5 in the Directive 67/548/EEC criteria).	Agree. It has been added.	
12/05/2010	Belgium / Frederic Denauw / Member State	STOT Rep. 2 – H373 (R48/22) : proposal based upon haematological findings (LOAEL in bold) -Rat 90d: 0, 50, 500, 5000, 50000 ppm (0, 3.5, 35, 351, 689, 3667 mkd) ¯RBC, Hb, Hct, -blood reticulocytes, MetHb, -spleen weight at 500-50000 ppm -Mouse 90d: 0, 50, 500, 5000, 10000, 50000 ppm (0, 10, 103, 1069, 2139, 11071 mkd) ¯RBC, Hb, Hct at 50000 ppm, -bilirubin at 500-50000 ppm, -dog 90d (97% purity): 0, 50, 500, 5000, 50000 ppm (0, 18, 163, 1961 mkd) ¯RBC, Hb, Hct, MCHC at 500-50000 ppm, -blood ret, MetHb, SulfHb at 5000-50000 ppm (-MetHb at wk9 only in f), -Kupffer cell pigment, BM hyperplasia at 500-50000 ppm, and -BM haemosiderose at 5000-50000 ppm) -dog 1yr 0, 10, 100, 500, 50000 pm (0, 0.36, 3.6, 19, 1888 mkd) ¯RBC, -MetHb, -BM hyperplasia, - BM-Kupffer cell -spleen haemosiderose at	FR: OK. Thank you.	Thank you for support. STOT RE 2 was considered but not concluded.

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		500-50000ppm, ¯Hb, -MCV, ¯MCHC, -ret, -platelets, -Sulf Hb at 50000 ppm It was of note that the most severe effects were generally observed at 5000-50000ppm, however slight effects were also seen at 500 ppm. The weight-of-evidence indicates that the threshold for classification STOT RE, H373 (10-100 mg/kg bw/d) was attained in rat and dog subchronic studies, and seems justified.		

Other effects - Environment

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
06/05/2010	Germany / Jan Averbeck / Member State	Environment The German CA agrees with the proposal for environmental classification and labelling of Flufenoxuron: according directive 67/548/EEC: N; R50/53 according regulation EC/1272/2008: Aquatic Acute 1 - H400 Aquatic chronic 1 - H410 M-factor: 10000 We would suggest the addition of signal word: Danger We would like to point out that the assessment of this substance (CA-Report) is not yet terminated and there is currently no approved final Assessment Report	FR: Thank you for your support FR: this information is given.	

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		available. Page 4: We recommend adding the proposed labelling (with wording of the hazard statements and precautionary statements) according to CLP Regulation. Additional remarks ref. chapter 4 environmental fate properties, point 4.3 Bioaccumulation: Measured bioaccumulation data (2 references) are summarized which indicates a very high potential for bioconcentration of Flufenoxuron in fish. The results of the BCF study with rainbow trout (Chapleo et al, 2003) BCF kinetic in whole fish of 25920 and 24187 has to be corrected for lipid content of test fish (3.7 %) to BCF 35027 and 32685 (lipid normalized to 5% lipid content). The results of the second BCF study with rainbow trout (Gill and Gould, 1990) could not be corrected for lipid content of test fish, because there are no data for lipid content of fish in the summaries of the report. The relevant calculated BCF kinetic are 15700 and 16130 (related to parent substance). Presumably was the uptake phase to short for reaching a steady state (equilibrium). The results of both BCF studies with rainbow trout could not be evaluated. The	Relevant labelling elements are included in the CLH report. FR: correction for lipid content was added for the Chapleo study.	Precautionary statements are not intended for harmonisation.

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		original studies (with raw data) are not yet available for authorities in Germany.		
11/05/2010	UK / Member State	We agree with the proposed environmental classification and labelling. However, as well as the M factor, specific concentration limits should be added. - Section 4.1.2: It would be useful to provide some further details of the ready biodegradation test (e.g. test substance concentration, inoculum source, etc.). - Section 4.1.3: Data should be compared to the classification criteria, rather than the substance being described as "potentially persistent". - Section 4.3.3: Data should be compared to the classification criteria, rather than the substance being described as "very bioaccumulable". - Section 7.2: There is no need to include terrestrial toxicity data since they are not used for classification purposes.	FR: the specific concentration limits were added. FR: more details concerning the conditions of the study were given. FR: a short comparison was added. FR: a short comparison was added. FR: we agree that this information are not used for classification purposes. Nevertheless, we prefer keeping this part to be harmonised with the other classification dossier.	Agree with UK. These results are not used for classification and are abundant in the classification dossier.
12/05/2010	Belgium / Frederic Denauw / Member State	Environment The substance Flufenoxuron is a very poorly soluble substance which shows acute toxicity at levels beneath the water	FR: thank you for your comments and your support.	No further comments.

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		solubility. Based on the results of the aquatic acute toxicity test on the most sensitive species (48hEC50Daphnia magna = 0.04 µg/L), the fact that the substance is not readily biodegradable and that the substance shows high potential to bioaccumulate (BCF = 25920), it is justified to classify as Aquatic Acute category 1 and Aquatic Chronic Category 1. Based on the classification and labelling criteria in accordance with dir. 67/548/EEC, Flufenoxuron should be classified as N, R50/53. In view of the proposed classification and the toxicity band between 0.00001 mg/l and 0.0001 mg/l, a M-factor of 10 000 could be assigned. In conclusion : we agree with the proposed environmental classification by the FR MSCA.		

Other effects - HH Repeat dose toxicity

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
06/05/2010	Germany / Jan Averbeck / Member State	Page 15-27 The French proposal to allocate STOT RE 2, H373 is supported with regard to the effects on red blood cells but not on	FR: Further haematological findings have been included for the 15 week- and 52 week-toxicity studies in dogs.	Thanks for support, classification STOT RE 2, H373 (red blood cells) was considered but not concluded

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		the liver. To further substantiate this proposal, more detailed information from the "Additional Report" that was submitted under 91/414/EEC to support inclusion of Flufenoxuron as an active compound in plant protection products in Annex I should be added to the CLH dossier. In particular, haematological findings should be reported in greater detail. Justification: The proposal STOT RE 2, H373 (corresponding to former risk phrase R48/22) is mainly based on haematological effects in Beagle dogs. In a 15-week study, methaemoglobinemia was observed at all dose levels (500, 5000, 50000 ppm) in females and at the two upper dose levels in males in week 9, i.e., at the first sampling time. Sulfhemoglobin formation was also noted more frequently in mid and high dose males. Furthermore, haemoglobin levels were significantly decreased in a dose-related manner in males at all dose levels (>10%). Also in males, red blood cell count, haematocrit and mean corpuscular heamoglobin concentration (MCHC) were decreased from 500 ppm onwards. In contrast, a statistically significant increase in reticulocytes was		

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		noted in both males and females at 5000 and 50000 ppm although there was no clear dose response. Mean corpuscular volume was higher in males at the two upper dose levels. At later time points (weeks 12 and 15), haematological effects were still apparent at the mid and high dose levels but were compensated at 500 ppm. However, bone marrow hyperplasia was observed at study termination in all treated dogs at 5000 and 50000 ppm and in 3 males and 2 females at the low dose level but not in the controls. Therefore, a NOAEL could not be established and the LOAEL was 18 (m) to 21 (f) mg/kg bw/day. In a one-year study in dogs, similar haematological and bone marrow findings were noted at the top dose level of 50000 ppm. At the next lower dose of 500 ppm (19-20 mg/kg bw/day), a lower red blood cell count, a lower MCHC and higher platelet count in male dogs, an increase in sulfhaemoglobin formation in females and bone marrow hyperplasia with pigment deposition in one female suggest a different susceptibility to the effects of this substance and confirmed a LOAEL in the range of 20 mg/kg bw/day. The NOAEL was 100 ppm		

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		(3.5/3.7 mg/kg bw/day). In sum, the findings suggest haemolytic anaemia and methaemoglobinaemia. MetHb formation, decrease in haemoglobin and histopathological findings (bone marrow, although not mentioned in the CLP regulation under 3.9.2.5.2) are sufficient for classification. Evidence of haematotoxicity was also obtained in a 90-day feeding study in rats with slight anemia and compensatory increase in heamatopoiesis occurring in females at 500 ppm (41 mg/kg bw/day) and above. The NOAEL was 50 ppm (4.1mg/kg bw/day). The liver effects were confined to high doses and/or were at least partly secondary to haematotoxicity (haemosiderosis, pigmentation). Therefore, these findings do not unequivocally point to specific organ toxicity (liver) at dose levels that were relevant for classification according to CLP criteria. More information would be helpful.	Agree: In the 15 week study in dogs, the increased kupffer cell pigmentation noted from 5,000 ppm could be considered as secondary to the haematotoxicity. In the 1 year study in dogs, increase in liver weights accompanied by increased incidences of hepatocellular fatty vacuolation were also observed but appeared at the highest concentration of 50,000 ppm (not relevant for classification) Therefore, we agree that liver effects should not be identified as a primary target organ although it may be secondary affected. The CLH report has been corrected accordingly.	
11/05/2010	UK / Member State	Repeated dose toxicity	FR: Further haematological findings have been	

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		Many of the changes reported do not include magnitudes. For example, on page 16 no details of the increased reticulocyte counts and decreased myeloid:erythroid ratios are given. This information should be provided in either the tables or text to enable an interpretation of their toxicological significance. This is particularly true for the dog studies, which form the basis of the classification proposal. Page 26/27. Summary and discussion of repeated dose toxicity. The RMS proposal to classify for repeated dose toxicity (Xn; R48/22) is based on the occurrence of anaemia in dogs (specifically, bone marrow hyperplasia and pigment deposition in the bone marrow and other organs at 18/21 mg/kg/d) and on hepatoxicity. Considering the anaemia, this was reported to be mild at 18/21 mg/kg/d, and the severity was not stated for the other dose groups. Additionally, it was transient in the lower dose groups, only becoming persistent at approximately 2000 mg/kg/d; for example, the reductions in haemoglobin were apparent in all treatment groups at week 9 but only in the high-dose group at week 15. Similarly, the increases in	included for the 13 week- and 52 week-toxicity studies in dogs.	Further data were provided by France. Classification STOT RE 2, H373 (red blood cells) was considered but not concluded

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<tr><th>Date</th><th>Country/ Person/Organisation/ MSCA</th><th>Comment</th><th>Response</th><th>Rapporteur's comment</th></tr>
<tr><td></td><td></td><td>methaemoglobin and sulfhaemoglobin by week 15 only occurred at 163/182 and 2000 mg/kg/d. Haemosiderin deposition also only occurred in the higher dose groups: from 163/182 mg/kg/d in the bone marrow, and from approximately 2000 mg/kg/d in the spleen and kidney (and in the latter two, only in 2/8 animals). Kupffer's cell pigmentation in the liver occurred in only 1/8 animals at 18/21 mg/kg/d.

Taking in turn each of the Directive 67/548/EEC criteria for classification as R48, as applied by the EU Working Group on Haemolytic Anaemia (Muller et al., 2006):

- Substance-related deaths. There were no substance-related deaths in any of the studies.
- Major functional changes in organ systems. There were no clinical signs of hypoxia indicative of anaemia.
- Any consistent changes in clinical biochemistry, haematology or urinalysis parameters which indicate severe organ dysfunction. All the recorded reductions in haemoglobin were < 20%. Additionally, by week 15 they were only apparent in the male 2000 mg/kg/d group. Haemoglobinuria and haemosiderinuria were not reported.</td><td>One criterion set in "Hazard classification of chemicals inducing haemolytic anemia: An EU regulatory perspective" by EU Working Group on Haemolytic Anaemia includes "marked increase of haemosiderosis in the spleen, liver or kidney in combination with other changes indicating significant haemolytic anaemia (e.g. a reduction in Hb at ≥ 10%) in a 28 day study"

In the 15 week-toxicity study in dogs, the following findings were observed:

<table>
<tr><td colspan="2">Histopathologica findings</td><td colspan="4">Dose levels (ppm)</td></tr>
<tr><td colspan="2"></td><td>0</td><td>500</td><td>5,000</td><td>50,000</td></tr>
<tr><td rowspan="2">Liver, pigmentation</td><td>M</td><td>0/4</td><td>0/4</td><td>4/4</td><td>4/4</td></tr>
<tr><td>F</td><td>0/4</td><td>1/4</td><td>3/4</td><td>4/4</td></tr>
<tr><td rowspan="2">Kidney, pigmentation</td><td>M</td><td>0/4</td><td>0/4</td><td>0/4</td><td>2/4</td></tr>
<tr><td>F</td><td>0/4</td><td>0/4</td><td>0/4</td><td>0/4</td></tr>
<tr><td rowspan="2">Spleen, pigmentation</td><td>M</td><td>0/4</td><td>0/4</td><td>0/4</td><td>1/4</td></tr>
<tr><td>F</td><td>0/4</td><td>0/4</td><td>0/4</td><td>1/4</td></tr>
<tr><td>Bone</td><td>M</td><td>0/4</td><td>0/4</td><td>0/4</td><td>4/4</td></tr>
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Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		- Severe organ damage noted on microscopic examination: Widespread or severe necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity. None of these effects was reported. Severe morphological changes that are potentially reversible but are clear evidence of marked organ dysfunction. Fatty vacuolation of hepatocytes was reported in dogs of the high-dose group in the one-year study, but no further details were given. - Generalised changes of a less severe nature involving several organs or severe changes in general health status. The increase in haemosiderosis in the spleen, bone marrow and kidney only occurred at levels above the classification guideline cut-off values. No clinical signs attributable to flufenoxuron exposure were reported. Considering the hepatoxicity, in dogs this was limited to slight effects on the liver: increased liver weights from 163/182 mg/kg/d in the 15-week study and 20 mg/kg/d in the 52-week study; and fatty vacuolation of hepatocytes from approximately 2000 mg/kg/d in the 52-week study. Liver effects were also observed in one of the mouse carcinogenicity study, in which higher	pigmentation The reduction in Hb > 10 % was observed in males only from 500 ppm at week 9. After 12 and 15 weeks, significant haematological effects were confined to the 50,000 ppm group male. Therefore, in this study, the effects are clearly evident at 5,000 ppm (163-182 mg/kg bw/d), dose higher than the threshold of CLP classification for prolonged exposure (100 mg/kg bw/d) and higher than the classification Xn; R48/22 for subchronic exposure (50 mg/kg bw/d). At 500 ppm (18-21 mg/kg bw/d), the haematological effects were considered as borderline: significant decrease in haemoglobin level observed in males only at week 9 and pigment deposition confined to the liver. Nevertheless, as a clear dose-response relationship was noted, this histopathological finding observed at 500 ppm could be considered as precursor effects. Based on the results above and taken into account the wide dose-spacing between 500 and 5000 ppm, sufficient serious effects are expected in the range of doses justifying a classification. Therefore, a classification: Xn; R48/22: Harmful: danger of serious damage to health by prolonged exposure if swallowed (CLP STOT RE 2 – H373) is proposed.	

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		liver weights, hepatic lesions, and microscopic changes such as an increased incidence of single cell necrosis occurred only at 7780 mg/kg/d, apart from Kupffer's cell aggregates which were increased from 739 mg/kg/d in females. Considering the CLP criteria, the guideline cut-off value for classification as STOT-RE 2 is ≤ 100 mg/kg/d (90-day study in rats). The only effects that occurred at a dose less than this guidance value and were persistent to week 15 in the 15-week dog study were bone marrow hyperplasia in 5/8 animals and Kupffer's cell pigmentation in the liver (1/8 animals), both of which were reported at 18/21 mg/kg/d; these effects do not meet the CLP criterion of "consistent and significant adverse changes in haematology" for classifying for haemolytic anaemia. Instead, they seem better to fit the evidence for no classification: "Small changes in haematology and/or transient effects, when such changes or effects are of doubtful or minimal toxicological importance." The increased liver weights (for which no further details were given) at 20 mg/kg/d in the 52-week dog study are not sufficient to support classification.	Concerning the hepatotoxicity, the increased Kupffer cell pigmentation noted from 5,000 ppm in the 15-week study in dogs could be considered as secondary to the haematotoxicity. In the 1 year study in dogs, increase in liver weights accompanied by increased incidences of hepatocellular fatty vacuolation were also observed but appeared at the highest concentration of 50,000 ppm (not relevant for classification) Therefore, the liver will be deleted as target organ for the proposed classification R48.	

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		In conclusion, the data presented do not support classification for repeated dose toxicity according to the Directive 67/548/EEC or CLP criteria.		
12/05/2010	Sweden / Helena Kramer / Member State	p.4. proposed classification: Repeated dose toxicity We agree that the proposed classification for repeated dose toxicity, Xn; R48/22 (CLP STOT RE 2 – H373), based on anemia and hepatotoxicity is justified. *Transferred from general comments by ECHA*	FR: Thank you. The mention of the liver effects has been deleted (see response to Germany comment)	Thanks for support, classification STOT RE 2, H373 (red blood cells) was considered but not concluded.
14/05/2010	Spain / Elina Valcarce / Member State	p 26 Summary and discussion of repeated dose toxicity The Spanish CA supports the proposed classification of flufenoxuron as Xn; R48/22 under Directive 67/548/EEC and as STOT Rep.2 – H373 under Regulation (EC) 1272/2008. Biochemical changes indicative of anaemia were present in dog 13 and 52 weeks studies from the dose level of 500 ppm (18-21 mg/kg/d). Changes in blood parameters (decrease in haemoglobin levels > 10 %) were associated with increased sulfhemoglobin and/or methemoglobin levels. Bone marrow hyperplasia and	FR: Thank you.	Thanks for support , classification STOT RE 2, H373 (red blood cells) was considered but not concluded

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		the presence of hemosiderin/ pigment deposition in bone marrow, liver, kidney and spleen were also observed from the same dose level. The effects occurred at a dose below the threshold of classification Xn; R48/22 of 50 mg/kg and below the threshold of classification STOT Rep.2 of 100 mg/kg for subchronic oral exposure and meet the classification criteria for risk phrase R48 set in "Hazard classification of chemicals inducing haemolytic anaemia: An EU regulatory perspective" by EU Working Group on Haemolytic Anaemia.		