Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Etofenprox

EC number: 407-980-2

CAS number: 80844-07-1

CLH-O-0000003158-74-01/A2

Adopted

28 November 2012

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: Etofenprox

EC number: 407-980-2
CAS number: 80844-07-1

General comments

Date	Country / Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
07/03/2012	Switzerland/ LKC Switzerland Ltd	Manufacturer/Applicant comments to CLH Report for proposal for Harmonisation Classification and Labelling of etofenprox based on Regulation (EC) No. 1272/2008 CLP Regulation Annex VI, Part 2. No Page Topic Comment 1 p. 8 below Table 1 "After discussion at the Biocides Technical Meeting the experts agreed upon 97.0% (w/w) as minimum purity" The value has deviated from Applicant proposed value. New value is acceptable.	Thank you!	The comments have been noted and considered in the evaluation.
		2 p. 35 4.4.1.4 last line "...not according to DSD criteria." Reword sentence to read '...not require classification according to DSD criteria.'	OK	
		3 p. 39 below Table 15 "in contrast, all 20 ----- a strong skin sensitizer" Delete paragraph as it is not necessary.	Information on positive control at this summary level of the evaluation is routinely requested at biocides TM in order to judge the validity of the	

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			results. Therefore we prefer to maintain the paragraph.	
		4 p. 56 Table 20a "Oral (gavage) developmental/fertility study; treatment of male P0: 9 weeks ----- gestation, analysis of P0 and F1 animals Change wording to " Oral (gavage) fertility study; treatment of male P0: 9 weeks ----- gestation, analysis of P0 animals and F1 fetus"	We will correct the last word, "F1 fetus" instead of "F1 animals". Given the fact that also F1 fetus is analysed we consider this study also as developmental study and maintain the title.	
		5 p. 56 Table 20a "Oral (gavage) developmental/fertility study; P0 treatment from d6 to d7---" Change wording to ,Oral (gavage) developmental study; P0 treatment from d6 to d7---'	Since F1 is followed up to form an F2 also fertility aspects are addressed in this study. Therefore we will maintain the title.	
		Typing changes: From -> To		
		6 p.24 Chapter number 1.1, 1.1.1 – 1.1.3 -> 3.1, 3.1.1 – 3.1.3	OK	
		7 p. 25 See table 3.1 -> See Table 11a	OK	
		8 p. 30 No fig. number -> Fig. 3.1	We insert "Figure 4.1.", since this figure is within chapter 4.	
		9 p.39 4.6.1.4 CLP Regulation table 3.4.4 for category 1B -> CLP Regulation table 3.4.2 for category 1	OK	
		10 p. 41 Table 17a Document IIIA 6.4.1.1_1 -> Document IIIA 6.4.1 11 p. 41 Table 17a Document IIIA 6.4.1.1_2 -> Delete	Since this was requested by ECHA we provided a new study summary for Green *et al.* (1983b), IIIA 6.4.1.1_2. By mistake this study summary was not included in the latest revised version. The numbering is correct.	
		12 p. 42 Table 17b NO(A)EL (mg/kg bw/day) -> NO(A)EL (mg/L) 13 p. 42 Table 17b LOAEL (mg/kg bw/day) -> LOAEL (mg/L)	OK	

Date	Country / Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		14 p. 46 Table 18a Document IIIA 6.6.3 -> Document IIIA 6.6.3/01	Four study summaries (doc IIIA) are in the dossier: doc IIIA 6.6.1 to 4. The Seeburg and Forster 1985b is not available as doc IIIA, therefore no sub numbering is carried out.	
		15 p. 48 Chapter number 4.11, 4.12 -> 4.10.1, 4.10.1.1	OK	
		16 p. 49 in Table 20 males and 250 females/group -> 20 males and 20 females/group	OK	
		17 p.56 Table 20a Document IIIA 6.8.1.1/1 -> Delete 18 p.56 Table 20a Document IIIA 6.8.1.1/2 -> Document IIIA 6.8.1.1 19 p.56 Table 20a Document IIIA 6.8.1.1/3 -> Delete	Since the study summaries (doc III) for all data summarized in the CLH report were requested by ECHA we provided all these new study summaries. By mistake these study summaries were not included in the latest revised version. The numbering is correct.	
		20 p.56 Table 20a ↓F1 --- (4% lower ---) -> ↓F1 --- (7% lower than control, not statistically difference)	From table 11 in study report it appears that bw at day 20 of gestation was 390 for control and 374.5 for group 4, which is a difference of 4%. We will indicate that bw and not bw gain is indicated and explain that this is not statistically significant.	
		21 p. 61 first sentence Above 238 mg/kg bs/day -> Above 238 mg/kg bw/day	OK	

Date	Country / Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		22 p.69 Table 21a Doc III A7.1.1.1.1/02 -> Delete 23 p.71 Table 21b Doc III A7.1.1.1.2/02 -> Delete	We don't see any benefit in deleting this information.	
		24 p. 77 1.1.4 -> 5.1.3	OK	
		25 p. 78 Table 21f Doc III A 7.3.1 -> Doc III A 7.1.3	OK	
		26 p. 83 Table 23a Doc IIIA 7.4.3.1 -> Delete reference	Reference changed to Doc III A7.4.1.1/03	
		27 p. 121, 132 Authors Ander-son -> Anderson	OK	
		28 p. 121 Authors Offer J. -> Offer J.M.	OK	
		29 p. 121 Authors Bottomley A -> Bottomley A. M.	OK	
		30 p. 121 Authors Dawe I.S.M -> Dawe I.S.	OK	
		31 p. 122 Authors Fisher B.J. -> Fisher B.R.	OK	
		32 p. 90 aquatic Acute 1, Study used LC50=0.027 mg/L -> LC50=0.0027 mg/L	OK	
		33 p. 90 aquatic Chronic 1, Study used: Doc III A7.1.1.2.1/02 EEC C.4-E (1984) -> EEC C6	OK	
		34 p. 90 aquatic Chronic 1, Study used: Doc III A7.1.2.2.2/01 28 and 18% -> 28, 18 and 19%	The 19% value is the result of a test vessel incubated under a light/dark cycle. Therefore the result was not used further.	
		35 p. 91 aquatic Chronic 1, Study used: Doc III A7.1.1.1.2/01 DT50=4.7 days, but not enough on toxic effects of two major metabolites -> DT50=4.7 days.	OK	
		36 p. 91 aquatic Chronic 1, Study used: Doc III A7.4.1.3/01 NOErC=(algae)=0.056 mg/L -> NOErC (algae)=>0.056 mg/L	OK	
		37 p. 91 DSD study used: Doc III A7.4.1.1/01 0.027 mg/L -> 0.0027 mg/L	OK	

Date	Country / Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		38 p. 91 DSD study used: Doc III A7.4.1.3/01 >0.0056 mg/L -> >0.056 mg/L	OK	
		39 p. 91 DSD study used: Dec III A7.1.1.2.1/02 EEC C.4-E (1984) -> EEC C6 *ECHA Comment: The attachment document is identical as in the table.*	OK	
09/03/2012	France / MSCA	We do not agree with the classification proposal of STOT RE 2 H373 (liver, kidney). We agree with the classification proposal for environment.	In our understanding the core question is, if LOAELs used for risk assessment are equally relevant for STOT RE C&L. If this is not the case a harmonization process into the one or other direction seems highly necessary to us. According to the CLP guidance "significant" changes should be in principle sufficient for defining a LOAEL for STOT RE 2 classification. However we are aware that different perspectives on the application of the new CLP regulation are available. We slightly extended our explanation and leave the further decision to the RMS.	Following evaluation of the available short- and longer term studies, RAC concluded that these reveal no biologically relevant effects warranting classification for repeated dose toxicity, neither under CLP nor DSD. The support for the proposed environmental classification is noted and is in line with RAC's conclusion.
12/03/2012	Denmark/ MSCA	DK supports the proposed harmonised classification for Etofenprox. DK furthermore suggests that Etofenprox is classified R64 according to the DSD.	It was our understanding that for applying the "additional" R64 phrase another human health classification is necessary according to the wording in DSD, Annex VI, Article 3.2.8. However we do not	The support and additional proposal is noted. As indicated above, RAC did not support classification for STOT RE, but the proposed classification for lactation and

Date	Country / Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
			have a strong view on this.	environmental effects was supported. In addition, RAC proposed R64 (allowed, as there is other classification proposed under DSD).

12/03/2012	Germany/ MSCA	The German CA thanks the Austrian CA for proposing the substance for harmonized classification. As you can see, we have some considerations in regard of the classification as H373 and some other small remarks. 1.3 Proposed harmonised classification and labelling based on Regulation (EC) No 1272/2008 If the AU-CA may agree to our argumentation below to not classify the substance "STOT RE 2; H373" we like to remark the following: Concerning the Precautionary statements we propose to omit P201 because we feel this statement is here not adequate/ too strict. As we have already "P308 + P313" we think "P314" can be omitted as well. On the other hand "(P102)" should be added in case the substance may be available for the consumer/ general public.	In case STOT RE2 will not be supported by the RAC we agree to your proposals with regard to P phrases. From our point of view, we could delete P314 in any case since P308+313 is presented.	Noted
		Doc II-A (version 02/2012), p. 15: We could comprehend your results for the classification of Etofenprox, but please have a look at the Doc II-A document included in the CLH dossier. It seems to us, that this version (02/2012) differs from the one we used when commenting the CAR (08/2011). In Doc II-A of the CAR, Tab. 1.6.2- on p. 18, an M-Factor of 1000 is applied to the classification Aquatic chronic 1, whereas in the Doc II-A included in the CLP-Dossier, Tab. 1.5.2 on p. 15, an M-Factor of 100 is applied to the classification Aquatic chronic 1. Please clarify. In our opinion it has been correctly laid out in the CLH report, that an M-Factor of 1000 is appropriate.	Thank you for your comment. In the Doc II-A version included in the CLP dossier the update according to the 2nd ATP of CLP was missing. Corrected.	Noted
12/03/2012	Sweden/ MSCA	SE supports classification of Etofenprox (Cas No 80844-07-1) as specified in the proposal. SE agrees with the rationale for classification into the proposed hazard classes and differentiations. The dossier was however hard to read and it was difficult to understand the rational behind the proposed classification. Therefore the text should be better structured and provide a more clear line of argumentation.	We amended the explanation for STOT RE2 classification. We agree that the evaluation is not easy to read due to the amount of available data and our intention to transparently describe all of them. However since the text was accepted for the CAR biocides report and the	The support is noted. As commented to the French comments above, RAC did not support classification with STOT RE, but the proposed classification for lactation and environmental effects was supported. In addition, RAC

			main points are summarized in the tables we would prefer not to change the wording.	proposed R64 (allowed, as there is other classification proposed under DSD).
12/03/2012	United Kingdom / UK CLPCA / MSCA	As a general observation, far too much consideration is given to NOAEL/NOEL and LOEL in the results tables and in the discussions throughout the dossier. This is distracting to the reader and makes it difficult to identify the key effects relevant to classification. These values are relevant to risk assessment, but not directly to hazard classification. p15. We question why R64 is not included in the proposal – see later comments.	We used the CAR for biocides to write this CLH report, therefore it may have information that is less relevant for CLH Dossier. However all relevant information is available. We attach further study summaries with this revised version. With regard to R64: It was our understanding that for applying the "additional" R64 phrase another human health classification is necessary according to the wording in DSD, Annex VI, Article 3.2.8. However we do not have a strong view on this.	Noted RAC agrees that R64 should be proposed as well.

Carcinogenicity

Date	Country / Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
12/03/2012	Denmark/ MSCA	DK supports the conclusion that classification for carcinogenicity is not warranted. Although the rat dietary study showed limited evidence for carcinogenicity (formation of thyroid microfollicles), the mechanistic study showed the mode of action was considered to be non-genotoxic and not relevant for human risk assessment.	OK	Noted

12/03/2012	United Kingdom / UK CLPCA / MSCA	We agree that there is limited evidence for carcinogenicity. However, it would help the reader if additional information were provided in this section. For example, additional information on the incidence of observed tumours and whether these were significant, historical control data on tumour incidences and a clearer explanation as to why the observed thyroid tumours are not considered to be relevant to humans; including a consideration of all available data (including rat, mice dogs) and the differences between male and female data. In addition there is again too much emphasis on NOAEL and LOAEL values in this section.	For more detailed information on the study outcomes please see the study summaries from the biocides CAR that were provided as attachment. Further study summaries are included with the revised version of this CLH report.	Noted

Mutagenicity

Date	Country/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
12/03/2012	United Kingdom / UK CLPCA / MSCA	From the discussion in section 4.9.4 and from looking at the DAR, we agree that the data do not support classification for mutagenicity. However, the test results appear to be missing from Table 18a and Table 18b. In section 4.9.5 (comparison with criteria) it is not clear why the reader is referred to Chapter 4.9	For more detailed information on the study outcomes please see the study summaries from the biocides CAR that were provided as attachment. We delete the reference to chapter 4.9.	Noted

Toxicity to reproduction

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
07/03/2012	Denmark / MSCA	We support with the classification regarding H362 – May cause harm to breastfed children.	OK	The support is noted and is in line with RAC's conclusion.
07/03/20	Switzerland/	*ECHA Comment: The comment below has been moved to this section*		The comments

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
12	LKC Switzerland Ltd	*from 'Other hazards and endpoints' because it refer to Toxicity to reproduction.* Proposal for Harmonised Classification and Labelling: Etofenprox • GHS classification proposal H362 – May cause harm to breast-fed children Proposal Manufacturer's comments CLH report p.9, p.13, p.16, p.45: Potential for accumulation in fat and hemorrhage effect in lactated rats observed in reproduction toxicity studies. However the observed effects are not considered to be specific developmental toxic effects but due to the naturally high ratio of milk uptake to bodyweight. We still have some concerns with the proposed classification of H362, as the incidences of hemorrhage were very low and some observations were not necessarily consistent with an effect on lactation In the "Guidance on the application of the CLP criteria" (Section 3.7) there are some comments on classification for lactation effects that suggest this classification for etofenprox might not be appropriate: "In general, positive data should usually be available to show that a substance leads to an adverse effect in offspring due to effects on lactation to support classification. "The mere presence of the substance in the milk alone, without a strong justification for a concern to offspring, would normally not support classification for effects on or via lactation." Although there are caveats in the guidance which permit classification when the above criteria are not met, we believe the strength of evidence for an effect on/via lactation by etofenprox is not sufficient to justify this. Further discussions were held at the 14th Meeting of the ECHA Committee for risk Assessment December 2010 (Room Document RAC/14/2010/69). The situation is still not clear.	We are aware that different perspectives on the translation of the new CLP regulation to practise are available. We hope that our line of arguments is clear in the report. From our understanding there is a potential for bioaccumulation. The decision will be taken by RAC and Commission.	have been noted and considered in the evaluation. RAC however concluded that the effects seen in offspring qualify for Lact. – H362/ R64.

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		In the mammalian metabolism studies, etofenprox was rapidly but partially absorbed after oral administration. It was uniformly distributed through the body, and transferred via placenta and via milk. There was no evidence of bioaccumulation; etofenprox was rapidly eliminated, mainly via faeces, a major part as metabolites.	In the LOEP of the biocides CAR we summarized the bioaccumulation potential as follows: "*Potential for Accumulation - Yes: Half-life time is l5 / 8.5 days (M/F) in fat.* *No accumulation in other tissues, tissue concentrations decline rapidly in all tissues except fat.* *Concentrations in liver, kidney, fat and muscle after 7 daily doses are 2.7 - 5.5-fold higher than after one dose, except female fat (13-fold higher)."*	
		In some studies, it was observed that etofenprox increases haemorrhagic diathesis in rodents and therefore it is difficult to deny possible effects of etofenprox on offspring. - However, increase of haemorrhagic diathesis was investigated in 13-week rat study (Report No. MTC 56/821067, 1983). As a result, it was considered that the increase was not due to direct effect of etofenprox on blood coagulation factors, but effect on liver function for synthesis of blood coagulation factors.	We are not sure, if the etiology of the haemorrhage would make a difference for the H362 proposal.	
		Hemorrhage effects were observed in the multi-generation study (Report No. MTC 67/85706, 1985), developmental neurotoxicity study (Report No. MTU 215/032731, 2003) and peri-/post-natal study (Report No. MTC 65/85423, 1985) (CLH p. 60 and 61). However the incidences were very low and some observations are not necessarily consistent with an effect on lactation.	In chapter 4.13.4. in the third paragraph from the end we correct/amend the information as follows:	
		A low incidence of ocular lesions / haemorrhages was found in the multi-generation study (Report No. MTC 67/85706, 1985), however the findings were considered inconsistent, i.e. they occurred in the	*.."Haemorrhagic lesions were observed at about 246 mg/kg bw/day (multigeneration study,*	

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		F1a litters but not in the F2b.	*0/4/30/246 mg/kg bw: at necropsy sum of subcutaneous haemorrhage and ocular defects 0/1/3/4 in F1a and 0/1/0/3 in F2a; no such findings were observed in F1b or F2b)"* From a statistical point of view it is to be expected that low incidence findings are not fully reproducible in all cohorts.	
		In the peri and post-natal reproductive study (PPN) (Report No. MTC 65/85423, 1985) the maternal animals were dosed by gavage at the unrealistically high dose of 5000 mg/kg/day. Although some pups at this dose level showed haemorrhage during the latter part of the lactation period (day 17 and 18), it should be noted that the oral absorption of etofenprox at this high dose level would have been relatively low, leading to significant elimination of unchanged etofenprox in maternal faeces which may have been a source of pup contamination.	*"subcutaneous haemorrhagic lesions at 5000 mg/kg bw/day (peri-/post natal study, before weaning, some pubs around nose)"* Contamination with maternal faeces containing etofenprox is an interesting argument.	
		In the DNT study (Report No. MTU 215/032731, 2003), the hemorrhage effects were only observed in young pups after 17 or 18 days of age when the pups would have been ingesting etofenprox with maternal diet.	*"... the major concerns are ocular lesions at 79 mg/kg bw/day (developmental neurotoxicity study, starting between days 16-21 of age with the majority occurring after weaning; at termination days 63-67; 238/79/28,4/0 mg/kg bw/day: 13/5/2/1 pups of ca. 180 each) and subcutaneous haemorrhagic lesions at 238 mg/kg bw/day (developmental neurotoxicity study, at termination days 63-67; 238/79/28,4/0 mg/kg*	

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			bw/day: 11/5/1/2 pups of ca. 180 each)" We agree with the observation that effects were observed after d16, but weaning was stopped at day 21 post partum and assuming adverse effects only from maternal diet may also be of low probability?	
12/03/2012	Spain / MSCA	p. 62. Comparison with criteria- Lactation Effects The Spanish CA supports the proposal of the dossier submitter to classify etofenprox under the CLP criteria as Lact. - H362: May cause harm to breastfeed babies, for its effects on or via lactation. In our opinion, this substance also fulfils the criteria defined in Annex VI of DSD in point 4.2.3.3., stating that substances which are known to accumulate in the body and which subsequently may be released into milk during lactation may be labelled with R33 "Danger of cumulative effects" and R64 "May cause harm to breastfeed babies". Therefore we propose to add R64 and R33 to the proposal of the dossier submitter. This proposal is based on the following effects observed in rats and rabbits: R64, Lact. - H362: May cause harm to breastfeed babies • In the toxicokinetics studies (Hawkins et al, 1985a), unchanged etofenprox was actively secreted into maternal milk and ingested by pups during the treatment period. Mean concentrations in naive pup stomach contents during treatment were 20 times higher than mean concentrations maternal plasma. The concentrations in pup stomach contents declined rapidly during the first 31 hours after cessation of treatment.	No comment	The comments and support have been noted, as well as the additional proposal for R64 and R33. RAC concluded that the effects seen in offspring qualify for Lact. – H362/R64. RAC did not support R33, as etofenprox does not have a particularly long half-life in fat.
		• Results in reproductive toxicity studies. - In two generations rat study (Cozen et al,1985c), the lower dose, at which alterations in peri-posnatal period (lactation) were described,	In order to avoid confusion: We named the Cozen et al 1985c study a peri-postnatal study	

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		was 5000 mg/kg b.w./day. At this dose it was observed a decrease of F1 pups weight, an increase of accumulated mortality 26,1% compared to control (accompanied by clinical signs as tremors and general motor inco-ordination) and kidney alterations.	since exposure was only from day 17 of pregnancy to day 21 post partum and a follow up without treatment up to F2 weaning. However the findings in the 5000 mg/kg bw day group should be considered with caution since this is 5 times above the limit dose proposed in the OECD TG 416.	
		- In a multi-generation study in rats (Cozen et al, 1985d) effects were seem during lactation at lower doses: at 246 mg/kg b.w./day (decreased weight gain in pups, increased thyroid weight, increased liver weight in all generations, increased kidney weight accompanied by histopathological alterations), and at 37/44 mg/kg b.w./day in male/female respectively (litter losses, increased thyroid weight, kidney histological alterations in 1 female, increased heart weight in 1 female; this last effect even with a lower dose 4,3/5,6 mg/kg b.w./day).	Reviewing the original study report again the following summary appears more precise (this corresponds to the shorter information in table 20a): 246 mg/kg bw day: ↓ mean litter weights from pp day8 on; some pups with body tremors, distended abdomen, abnormal gait during late lactation, some of the affected pups died, 2 total litter loss in first mating second half of lactation; ↑ kidney weights accompanied with histo/pathological alterations; ↑ liver weight accompanied with histopathological alterations, ↑ heart weight in weanlings; unclear effects on thyroid weight of F1 and F2 animals and ↑ height of follicular epithelium in 6/23 F1B males; 37 mg/kg bw day: ↑ kidney weight only with adult F2B females; ↑ liver weight in	

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			weanlings (F1A m & f, F2B m & f, F1B m) but not adults; adverse kidney histology in 1 female 4.3 mg/kg bw day: NOAEL However as discussed in the paragraph below table 20b, the findings in the mid dose group are not considered sufficiently reliable for C&L or AEL derivation.	
		- In the teratogenicity studies in rats (Cozen et al, 1985a, Cozen et al, 1985b) and rabbits (Bottomley et al, 1985; Fisher et al, 2000) adverse effects were observed at 250-300 mg/kg b.w./day (increased post-implantation loss and decreased weight gain in rabbit pups during lactation).	In the rat studies only at the very high dose of 5000 mg/kg bw day minimal adverse effects were observed. In the rabbit studies adverse effects were observed at 250 or 300 mg/kg bw day, but only in the presence of maternal toxicity (see 2nd and 3rd paragraph after table 20a).	
		- In a neurotoxicity/teratogenicity study in rats (Myers et al, 2003), effects were described in lactation period (intraocular hemorrhage in one female pup, and functional alterations in male pups at maternal doses of 79,2 mg/kg b.w./day).	At 79 mg/kg bw day ocular lesions were observed in 5 pups: 238/79/28,4/0 mg/kg bw/day: 13/5/2/1 pups of ca. 180 each) and subcutaneous haemorrhagic lesions at 238 mg/kg bw/day (238/79/28,4/0 mg/kg bw/day: 11/5/1/2 pups of ca. 180 each)	
		R33: Danger of cumulative effects. - On the basis of the physicochemical properties of a substance we can estimate its lipophilicity and bioaccumulation potencial. Etofenprox has a high Low Pow value, equal to 6,9 at 20ºC ± 1ºC	From a formal point of view R33 is described within "Article 3.2.8. Other toxicological properties" and therefore in our	

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		(Tognucci A, 1998e), which indicate that it is a highly lipophilic substance, with ability to accumulate in fat. - The toxicokinetics studies (Hawkins et al, 1985a) indicate that etofenprox absorbed from the gastrointestinal tract reaches its highest concentration in fat and other tissues with a high fat percentage (e.g. pancreas, mammary gland). In this study, concentrations declined rapidly in all tissues at 24 h except for fat and pancreas, in which, significant amounts appear even 240 h after treatment. The decline rate in mammary gland was slower than in other tissues and the substance persisted until 120 h (last time studied in this report). The capacity of bioaccumulation of a substance following repeated maternal exposure may be an important factor to consider, because this may contribute to a maternal body burden that leads to a potentially toxic level in the offspring. It seems to be necessary a bioaccumulation of etofenprox in the maternal body, particularly in fat tissue for adverse effects to occur during lactation in the offspring.	understanding R33 may just like R64 only be applied if there are other human health classifications.	
		In view of these considerations, the Spanish CA considers that the risk phrases R 64, Lact. - H362: May cause harm to breast-fed children and R33: Danger of cumulative effects, should be allocated, due to, the high concentration in fat, pancreas and mammary gland that would produce the bioaccumulation of etofenprox in the maternal body, the significant excretion via maternal milk and the adverse effects during lactation (increase in postnatal mortality, clinical signs, kidney lesions, ocular findings and lower body weight gain) seen in the offspring of rat reproduction studies and in the rat developmental neurotoxicity study.	Please see above, from a formal point of view we think that we can classify etofenprox only according to GHS.	
12/03/2012	Germany/ MSCA	Lactation According to CLP a classification for lactation effects shall be based on a total weight of evidence evaluation based on results from one or two generation studies in animals which provide clear evidence of adverse effects in the offspring due to transfer in the milk or adverse effect on the quality of the milk and/or ADME studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk. The potential for accumulation in fat and active secretion into milk	We agree that a total weight of evidence evaluation is necessary to evaluate lactation effects. Our conclusion from the data presented in the CLH report is different, but we are clearly ready to follow a different international agreement.	The comments have been noted. RAC however concluded that, all in all, the effects seen in offspring qualify for Lact. –

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		was observed within toxicokinetic studies (Hawkins et al., 1985a). However, DE questions whether a reduced body weight development of the pups at the highest dose level meets the criterion to classify for Lact.; H362 (May cause harm to breast-fed children). Also the effect occurred in the presence of some maternal toxicity (kidney effects). Haemorrhage effects in lactated rats are of low incidence (Cozens et al., 1985d).		H362/R64.
12/03/2012	Sweden/ MSCA	In general SE agree with the conclusion that Etofenprox should be classified for H362 – May cause harm to breast-fed children based on: - ADME data showing that transfer to milk occur and that etofenprox concentrations in pup-stomach content is >20 times higher than in maternal plasma - increased pup-mortality occur during late lactation - the occurrence of effects in liver, kidneys and subcutaneous/ocular bleeding in pups – lesions similar to those occurring in adults either in the maternal generation or in repeated dose toxicity studies. An additional reason for concern is that the substance also seems to meet the PBT-criteria. All this warrants a classification and labeling to inform that lactating women should avoid exposure of this substance.	Please note that a PBT assessment has been performed for the Biozides CAR (still under preparation) on Etofenprox PT18. This assessment shows that neither Etofenprox nor its major degradation products are PBT substances, since they don't meet the P criterion.	The support is noted and is in line with RAC's conclusion that the effects seen in offspring qualify for Lact. – H362/ R64.
		The dossier was hard to read and it was difficult to understand the rational behind the proposed classification. Therefore the text should be better structured and provide a more clear line of argumentation. The decision to support the suggestion could not be made by only reading through the section 4.13 Toxicity for reproduction, it required looking into the study summaries. Due to lack of time we have, however, not been able to go to the bottom with some issues of our concern. In some instances it is not clear on what basis the conclusions were drawn, e.g. how a difference between control group 0.6% and high dose group 5.7 % could be considered "marginal".	Myers et al. 2003 (dev. Neurotox study): At 2100ppm, a treatment-related marginal increase in pre-weaning mortality occurred between days 14 and 21, during which time 5.7% of progeny died compared with 0.6% of the control progeny. However, overall pup mortality to	Noted

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
			weaning was comparable in all treated and control groups. Pre-weaning survival between days 14 and 21 was unaffected by treatment at 250 and 700ppm.	
		Page 56-57: We would suggest that the same information is given for all studies in column 1 of Table 20a – that is include exposure information for all studies. Page 61: We do not agree with the conclusion in the first paragraph on page 61 that the increased pup-mortality is of low level of concern. The late pup-mortality appears to be one of the reasons why the substance needs to be classified for H362.	OK, we amend the table. With regard to pup-mortality see our comment above. We would not give a high weight to this finding, but nevertheless support the H362 proposal.	
12/03/2012	United Kingdom / UK CLPCA / MSCA	p56. Table 20a. It would be helpful to the reader if it were clearly stated which effects were relevant to the adults and which were relevant to the pups.	The suffixes a, b and c indicate the NOAEL for parental, reproductive and developmental effects, the respective LOAELs and effects are indicated in the same line.	The comments and support have been noted. RAC concluded that the effects seen in offspring qualify for Lact. – H362 and also for R64 (is indeed allowed, as there is other classification proposed under DSD).
		p58. Line 3. The post implantation loss in rabbits is described as 'slightly increased' (10.1% vs 4.3% in controls) – is this statistically significant or not, and does it fall within the historical control range?	The post implantation loss was not statistically significant in this study. No historical control data were submitted. In general post-implantation loss usually shows high variability in historical controls and is	

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
			typically considered an adverse effect only when it reaches levels that are <u>at least</u> double that observed in concurrent controls (Hood 2006, Developmental and Reproductive Toxicology, CRC press, p369)	
		p63. Section 4.13.6 - we agree with the proposed classification for H362: may cause harm to breast-fed children.	OK	
		p63. In section 4.13.6 (conclusions on classification and labelling), non-classification for R48 is discussed in the context of dismissing R64. However, as mentioned above, it is not clear why R64 can not be applied given that it is proposed to classify with N; R 50-53. It is our understanding that it is possible to apply R64 when a classification is proposed (i.e. there is an indication of danger), not only where a human health classification is proposed.	It was our understanding that for applying the "additional" R64 phrase another human health classification is necessary. However we do not have a strong view on this.	
12/03/2012	Denmark/ MSCA	*ECHA Comment: The comment below has been moved to this section from 'Other hazards and endpoints' because it is refer to Toxicity to reproduction.* DK furthermore suggests that Etofenprox is classified R64 according to the DSD. In the CLH report for Etofenprox it is argued that classification with R64 may only be applied in addition to other human health R phrases – which are not applicable. However, according to our interpretation the criteria for application of R64 are fulfilled. According to the DSD, R64 may also be applied to substances that are not toxic to reproduction but where o toxicokinetic studies indicate likehood of toxic levels of the substance in breast milk and/or o the results of one or two generation studies in animals indicate the presence of adverse effects on the offspring due to transfer in the milk and/or o evidence in humans indicate a risk to babies during the lactational period	It was our understanding that for applying the "additional" R64 phrase another human health classification is necessary according to the wording in DSD, Annex VI, Article 3.2.8. However we do not have a strong view on this.	The additional proposal for R64 is in line with RAC's conclusion.

Date	Country / Organisation / MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		As the toxicokinetic studies indicate potential for accumulation in fat and secretion into milk and the peri/post natal study with rats indicate adverse effects on offspring that could not be attributed to specific developmental effects, classification with R64 is considered justified. It is also noted that in a peer review of the Draft Assessment Report for Etofenprox, the European Food Safety Authority (EFSA) has concluded that the classification R64 and R50/53 (Dir. 67/548/EEC) is justified (EFSA, 2008).	In the latest DAR publically available (August 2007) it is explicitly mentioned that the RMS considers the application of R64 inappropriate. The latest public available EFSA review report (October 2009) does not mention any C&L proposal.	

Respiratory sensitisation - no comments received

Other hazards and endpoints

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
05/03/2012	Spain / MSCA	We are in agreement with the classification for environmental hazards proposed by Austria	Thank you!	Noted.
07/03/2012	Switzerland/ LKC Switzerland Ltd	Proposal for Harmonised Classification and Labelling: Etofenprox • GHS classification proposal STOT RE 2, H373 – May cause damage to organs (liver, kidney) through prolonged or repeated exposure. Proposal Manufacturer's comments p. 9, p.16, p. 45; Classification for H373 is required in case subchronic NOAELs are between 10 and 100 mg/kg bw day. Due to large dosing step in the 90 day rat study the respective LOAEL of 120 mg/kg bw day (liver histology, weight, disfunction) may be well below 100 mg/kg bw (NOAEL at 20 mg/kg bw day). The maternal LOAEL of the developmental neurotoxicity study is with 79 mg/kg bw/day below 100 (transient retardation of gestation weight gain by 14% from day 6 to 10). The LOAEL in the 2-year rat study at 26 mg/kg bw day (liver histopathology effects) and in the 2-year mouse study at 10 mg/kg bw day (kidney histopathology effects) are well below 100 mg/kg bw day, also if multiplied by 2 for accounting the longer exposure duration. We do not agree with the proposed classification of STOT RE 2 (H373)	In our understanding the core question is, if LOAELs used for risk assessment are equally relevant for STOT RE C&L. If this is not the case a harmonization process into the one or other direction seems highly necessary to us. According to the CLP guidance "significant" changes should be in principle sufficient for defining a LOAEL for STOT RE 2 classification.	The comments have been noted and considered in the evaluation of the available short- and longer term studies. RAC concluded that these studies reveal no biologically relevant effects warranting classification for repeated dose toxicity, neither under CLP nor DSD.
		According to paragraph 3.9.2.9.5 of Annex I to Regulation 1272/2008 (16 December 2008), the guidance values to assist category 2 classification should be extrapolated, up or down, to take account of the duration of treatment. Thus, the guidance value (C) of 10 < C < 100 mg/kg/day shown in the guidance refers to a 90-day oral rat study. Therefore, for effects that occurred after at least 104 weeks treatment in the rat and mouse oncogenicity studies, the guidance values should be reduced by a factor of 8. The relevant guidance value is 1.2 < C < 12.5 mg/kg/day.	We agree that according to Haber´s rule a factor of 8 would apply for extrapolating from 13 to 104 weeks. However the factor of 2 was considered since it is mentioned in the REACH guidance R8 for the assessment factor for extrapolating from sub-	

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
			chronic to chronic exposure. This is supported by literature data indicating that up to 190 respective NOAEL ratios have a geometric mean between 1.5 to 2.3., depending on the analysis (Schneider et al 2006. Reg. Tox. Pharm. 44/2, 172-81 and Bokkers BG, Slob W. 2005 Toxicological Sciences 85, 1033-1040). However we agree that available sub-chronic LOAELs should be of primary relevance for STOT RE C&L discussions.	
		In the rat oncogenicity study (Report No. MTC 59/85581, 1986), the lowest dose level at which hepatic effects occurred was 700 ppm (equivalent to a mean dose of 25.5 mg/kg/day). The effect, eosinophilic hepatocytes occasionally associated with vacuolation, occurred only in males, only after 106 weeks treatment and in the absence of other hepatic histological changes. The dose at which it occurred was approximately twice the guidance value, C. Therefore, a STOT RE 2 classification for liver effects is not warranted on the basis of this study.	We agree that at the LOAEL of this study no severe effects were observed. However we were of the opinion that a LOAEL based on "significant" findings and considered relevant for AEL derivation and risk assessment should also be relevant for C&L. Please note that we would propose an assessment factor of 2 for chronic- to sub-chronic exposure extrapolation which would result in a LOAEL below the guidance value.	
		Consideration of data from the 13-week oral study in the rat (Report	In the CLH report it is	

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		No. MTC 56/821067, 1983) also suggests that a STOT RE 2 classification for liver effects is not warranted since the lowest dose at which liver effects were apparent was 120 / 142 mg/kg/day, in males and females, respectively.	mentioned that due to the large dose spacing (male NOAEL/LOAEL = 20/120 mg/kg bw day) the "real" LOAEL may be well below the upper boundary of the guidance value of 100 for STOT RE.	
		In the mouse oncogenicity study (Report No. MTC 59/85582, 1986), the lowest dose level at which renal effects occurred was 100 ppm (equivalent to 10.4 and 11.7 mg/kg/day, in males and females, respectively). At this dose, renal effects were not evident after 26 or 52 weeks treatment. The effect at 100 ppm was a marginal increase in the incidence of dilated or basophilic renal tubules (12/52 vs. control incidence of 7/52), but was not associated with dilated/cystic Bowman's capsule, dilated medullary tubules, focal tubular loss and prominent interstitial papillary tissue, as occurred at the highest dose level employed (4900 ppm). These findings suggest that the ingested dose levels at 100 ppm (10.4 or 11.7 mg/kg/day) were very close to the NOAEL. Although they are slightly lower than the upper guidance value of 12.5 mg/kg/day,	According to the study summary also the renal effects in females may be considered; m & f combined incidences of dilated or basophilic renal tubules would then appear as: 19/104 vs. control incidence of 11/104. We agree that at the LOAEL the effects were not severe, however they were significant. Please note that we would propose an assessment factor of 2 for chronic- to sub-chronic exposure extrapolation which would result in a LOAEL below the guidance value.	
		consideration of data from the 13-week oral study in the mouse (Report No. MTC 55/821112, 1983) suggests that a STOT RE 2 classification for kidney effects is not warranted because the lowest dose at which kidney effects occurred was 1975 / 2192 mg/kg/day, in males and females, respectively.	We agree that the subchronic mouse data do not support STOT RE classification.	
		The guidance values applicable to a 90-day oral rat study, 10 < C < 100 mg/kg/day, are also applicable to the rat multi-generation study (Report No. MTC 67/85706, 1985). In this study, histopathological	We agree that the multi-generation study does not support STOT RE	

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		renal alterations occurred almost exclusively at 4900 ppm (equivalent to 210 – 730 mg/kg/day), but one F1b adult female at 700 ppm (equivalent to 95 - 48 mg/kg/day) showed cystic collecting ducts. There was no cortical involvement and no associated congestion, fibrosis, scarring and inflammation as seen at 4900 ppm. Although F2b generation female kidney weights were significantly higher than control, the difference amounted to 7.2% and the kidney weights of all other generations, weanlings and adults, were comparable to control values. There were no treatment-related hepatic alterations at 700 ppm in this study. Based on one animal (1/24 = 4.2%, or 1/47 males and females = 2.1%) at 700 ppm (95 - 48 mg/kg/day) with a possible treatment-related kidney lesion there is no justification for a STOT RE 2 classification.	classification. This was mentioned in an earlier draft CAR version, but not in the latest versions of draft CAR and CLH dossier. In contrast the LOAEL of the developmental neurotoxicity study (79 mg/kg bw day; transient retardation of gestation weight gain by 14% from day 6 to 10) may be considered for discussing classification for STOT RE 2.	
		In conclusion, data from the rat and mouse oncogenicity studies and the rat multi-generation reproduction study do not support a STOT RE 2 (liver/kidney) classification for etofenprox because the possibility of substantial hepatic or renal toxicity at dose levels less than the upper guideline limit is highly unlikely. Data from the rat and mouse 13-week oral studies support this view. *ECHA Comment: Part of the comment has been moved to 'Toxicity to reproduction' as it refers to Toxicity to reproduction. The attachment document is identical as in the table*	Our WoE conclusion would be different, but we fully respect divergent views on this. Our understanding is that the core question is, if LOAELs used for risk assessment are equally relevant for STOT RE C&L. If this is not the case a harmonization process into the one or other direction seems highly necessary to us. According to the CLP guidance "significant" changes should be in principle sufficient for defining a LOAEL for STOT RE 2 classification.	
07/03/2012	Denmark / MSCA	We do not support the proposed classification with STOT RE category 2; H373 - May cause damage to organs (liver, kidney) due to the effects seen on the liver.	Our understanding is that the core question is, if LOAELs used for risk	Following evaluation of the available short- and longer

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		The effects on the liver was minimal and do not fulfilled the criteria for the STOR-RE as being significant or severe toxicity with functional disturbance or morphological changes toxicologically relevant (expect for the NOAEL levels).	assessment are equally relevant for STOT RE C&L. If this is not the case a harmonization process into the one or other direction seems highly necessary to us. According to the CLP guidance "significant" changes should be in principle sufficient for defining a LOAEL for STOT RE 2 classification.	term studies, RAC concluded that these reveal no biologically relevant effects warranting classification for repeated dose toxicity, neither under CLP nor DSD.
		The liver effects were confined to changes in liver weights (bw changes as well) often without histopathological correlates, the fatty change observed in the liver was minimal. The liver dysfunction mentioned seems to be based upon minor changes in clinical chemistry in cholesterol in male rats in the 90 days study only (and not as stated in the CA-report on clinical signs which was not observed in the study). In the chronic rats study increased liver and hepatocytenlargement was seen in the highest doses (187 mg/kg bw/day) The main target organ was not the same in both species, main target organ in rats was the liver while in mice the kidney. With respect to the kidney effects found in mice we suggest it should be discussed whether one species is enough for classification. In adult mice the kidney effects was manifested as increased incidence of dilated / basophilic renal cortical tubules beginning from 10.4 mg/kg bw/day (NOAEL 75 mg/kg bw/day) and the increased mortality in males in the 110- week dietary. The increased mortality in males is considered by the RMS to be due to the renal lesions. No other consistent findings were observed in biochemistry or urine analysis except from "treatment-related effects on urine parameters were confined to a larger volume of more dilute urine in male treated groups in week 52 and reduced urine specific gravity in males at 4900ppm in weeks 77 and 102"	Your statements are correct. Also in the CAR the wording was corrected to clinical chemistry effects; besides cholesterol also GPT and GOT and T4 values were significant, see the study summary for details (doc IIIA6_04_1_1) The NOAEL in the 108 week mouse study is 3.1 mg/kg bw day.	

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
09/03/2012	France / MSCA	STOT RE 2 H373 (liver, kidney): we consider that the weight of evidence is not sufficient to propose this classification. Justification: For liver, the effects observed in the 13-week dietary toxicity study in rats are considered as adaptive responses due to an increase of enzyme induction. According to the Guidance on the Application of Regulation (EC) No 1272/2008, no classification would be appropriate. For kidney, the effects observed in the 13-week dietary study in mice effects appeared at very high doses (1975/2192 mg/kg bw/day) and are not considered sufficiently severe to require classification. Similarly, in the 2-year mice study, the effects on the kidneys observed at the LOAEL are considered as minor. Even if the incidence and the severity of effects increased with the dose, relevant effects appeared at dose higher than the threshold for classification. Finally, the developmental neurotoxicity study is not considered relevant to propose a classification STOT RE since only transient retardation of gestation weight gain was noted at the LOAEL. In conclusion, we think that the severity of the observed effects in the repeated dose toxicity studies is not sufficient to reach a classification STOT RE 2 H373 (liver, kidney).	In our understanding the core question is, if LOAELs used for risk assessment are equally relevant for STOT RE C&L. If this is not the case a harmonization process into the one or other direction seems highly necessary to us. According to the CLP guidance "significant" changes should be in principle sufficient for defining a LOAEL for STOT RE 2 classification.	Following evaluation of the available short- and longer term studies, RAC concluded that these reveal no biologically relevant effects warranting classification for repeated dose toxicity, neither under CLP nor DSD.
		Environmental¬ hazards We agree with the current proposal for consideration by rac: CLP regulation: Aquatic acute 1 (M=100); Aquatic chronic 1 (M=1000); H400 – very toxic to aquatic life; H410 – very toxic to aquatic life with long lasting effects. DSD: N; R50-53 – very toxic to organisms, may cause long-term adverse	Thank you!	Noted

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		effects in the aquatic environment.		
12/03/2012	Spain / MSCA	p. 45. Summary and discussion of repeated dose toxicity findings relevant for classification as STOT RE Based on the comparison of repeated dose toxicity data with DSD and CLP classification criteria, the Spanish CA agreed with the dossier submitter proposal not to classify etofenprox for repeated repeated dose toxicity according to DSD. However, in our opinion the repeated dose toxicity findings observed in liver and kidney do not warrant the classification for specific target organ toxicity proposed by the dossier submitter (SOT-RE 2 H373). The CLH report seems not detailed enough. The incidence and severity of effects observed in the repeated dose studies are not reported sometimes. These effects were often transient and not significant or were observed in controls as well.	In our understanding the core question is, if LOAELs used for risk assessment are equally relevant for STOT RE C&L. If this is not the case a harmonization process into the one or other direction seems highly necessary to us. According to the CLP guidance "significant" changes should be in principle sufficient for defining a LOAEL for STOT RE 2 classification.	Following evaluation of the available short- and longer term studies, RAC concluded that these reveal no biologically relevant effects warranting classification for repeated dose toxicity, neither under CLP nor DSD.
12/03/2012	Denmark/ MSCA	DK agrees with the proposed classification of Etofenprox with STOT RE 2; H373 H362 Aquatic acute 1; H400 (M = 100) Aquatic chronic 1.; H410 (M = 1000) / DSD classification: N; R50/53 *ECHA Comment: Part of this comment has been moved to 'Toxicity to reproduction' because it is referring to Toxicity to reproduction.*	OK Thank you!	The support is noted. As indicated earlier, RAC did not support classification for STOT RE, but the proposed classification for lactation and environmental effects was supported. In addition, RAC proposed R64 (allowed, as there is other classification proposed under DSD).
12/03/2012	Belgium/ MSCA	environment : Based on the results of the aquatic toxicity test on the most sensitive species (Dapnia magna 48hEC50=0.0012mg/l;	Thank you!	The support is noted and is in line with RAC's conclusion.

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		21dNOEC=0.000054mg/l) the fact that the substance is considered as not rapidly degradable it is justified to classify, following the classification criteria of the 2nd ATP, as Aquatic Acute 1, H400 and Aquatic chronic 1,H410. Furthermore, the substance shows high potential to bioaccumulate (BCF >500), In view of the proposed classification and toxicity band for acute toxicity between 0,001 and 0.01 mg/l, an M-factor for acute toxicity of 100 could be assigned, and an M-factor for chronic toxicity of 1000 (not rapidly degradable substance and chronic toxicity band between 0.00001 and 0.0001 mg/l). Based on the classification and labelling criteria in accordance with dir. 67/548/EEC, Etofenprox should be classified as N,R50/53 In conclusion: we agree with the proposed environmental classification by the Austrian MSCA. Some editorial or/and minor comments: • Environmental hazard assessment: it would be clearer when the tables with the overview of the performed tests are listed first, followed by the descriptive text. • p. 13and p92: Please delete the precautionary statements in the proposal as they need not to be specified in a CLH report. They will not be included in annex VI and the final responsibility for the allocation of P statements lies with the supplier.	On p. 13 and 92 is a complete proposal for C&L. The proposal without P statements to be considered by RAC can be found on page 9.	
12/03/2012	Germany/ MSCA	p. 89 and 90, Chapter 5.4: Please correct under the heading "Studies used": LC50 (fish) = 2.7µg/l= 0.0027mg/l (p. 89), as well as ErC50 (algae) >56.25 µg/l= 0.056mg/l (p. 90).	OK	Noted
		Repeated dose toxicity In our opinion, it is not appropriate to classify for STOT RE 2; H373 (May cause damage to organs (liver, kidney)). In the 90-day rat study the severity of the described effects (liver histology, weight, disfunction) is minimal and the incidence is low at the dose level of 120 mg/kg bw/day (LOAEL).	In our understanding the core question is, if LOAELs used for risk assessment are equally relevant for STOT RE C&L. If this is not the case a harmonization	Following evaluation of the available short- and longer term studies, RAC concluded that these reveal no biologically

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		The same applies to the 2-year rat study (liver histopathology effects) and the 2-year mouse study (kidney histopathology effects). The observed effects do not occur with an incidence and severity at a dose level that a classification is justified.	process into the one or other direction seems highly necessary to us. According to the CLP guidance "significant" changes should be in principle sufficient for defining a LOAEL for STOT RE 2 classification.	relevant effects warranting classification for repeated dose toxicity, neither under CLP nor DSD.
12/03/2012	Sweden/ MSCA	For the environmental classification another concern is that the substance also seems to meet the PBT-criteria.	We always understood that C&L is one issue and that PBT is a completely different issue. A PBT assessment has been performed for the Biozides CAR (still under preparation) on Etofenprox PT18. This assessment shows that neither Etofenprox nor its major degradation products are PBT substances, since they don't meet the P criterion.	Noted
12/03/2012	United Kingdom / UK CLPCA / MSCA	Acute Toxicity: We agree that the data do not support classification for acute toxicity. Skin Irritation: We agree that the data do not support classification for skin irritation Eye Irritation: We agree that the data do not support classification for eye irritation.	OK	Noted Noted Noted
		A classification for STOT-RE 2 (liver, kidney) under the CLP Regulation is proposed, with no classification under DSD. At present, there is insufficient information in the dossier for the reader to make a decision on this proposed classification.	We are sorry, but we had to use the CAR for biocides to write this CLH report, therefore it may have	The comments have been noted and considered in the evaluation of the

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		In the tables on p41 and 42, less emphasis should be given to NOAEL and LOAEL values, as these are not directly relevant for classification. To allow the reader to make a decision on classification (under both CLP and DSD) further information is needed on the adverse effects seen in the animals (e.g., the magnitude of the increases in liver weight) and the dose levels at which these effects were observed.	information that is less relevant for the CLH Dossier. However we think that the NOAEL and LOAELs are quite relevant for STOT RE classification and all relevant information is available with further details in the attached study summaries. Please note that magnitude and incidence information is not even summarized in the original study reports in all cases.	available short- and longer term studies. RAC concluded that these studies reveal no biologically relevant effects warranting classification for repeated dose toxicity, neither under CLP nor DSD.
		The consideration of repeated dose toxicity is spread across two sections of the dossier – section 4.7 (repeated dose toxicity) and section 4.12 (carcinogenicity). On p44, for the summary and discussion of the repeated dose toxicity findings in accordance with the DSD criteria, the reader is referred to sections 4.10 and 4.11, however these are just titles on p48. It would assist the reader if the summary and discussion of the repeated dose toxicity findings were discussed in 4.7.5 to 4.7.7 (albeit with reference to the carcinogenicity studies in Section 4.12).	Thank you, we correct the chapter references.	
		P44. It is not clear why R64 is discussed in section 4.7.7 – there are no studies relating to effects during lactation in the repeated dose toxicity section. This effect should be (and is already) discussed in sections 4.13.5 and 4.13.6.	Ok, we delete the R64 and the H362 conclusion in these chapters.	
		P44. Section 4.7.7 states that no classification is given for R48/20/21/22 because the guidance value for classification is lower than the guidance value for classification under the CLP Regulation. Whilst the guidance value for classification is lower, this alone does not explain why the substance does not meet the criteria for classification. Section 4.7.6 should be used to compare the effects seen in the animals at doses relevant for classifcation with the DSD classification criteria and a conclusion drawn on this basis. Where no effects were	Ok, thank you. In our understanding the criteria for R48 and STOT classification are basically the same with the exception that the guidance values were lowered. We introduce a reference to	

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		seen at doses relevant for classification this should be clearly stated.	chapter 4.8.2.	
		P45 Section 4.8.2 - It is stated the LOAEL is multiplied by 2 to account for the longer exposure duration – this is not the correct application of Haber's rule. To obtain the guidance value for a 2 year study, you would need to divide the guidance value for a 90 day study (100 mg/kg bw/d) by 8 (= 12.5mg/kg bw/d). The effects in the kidneys seen at 10 mg/kg bw/d in the 2 year mouse study should be considered accordingly (i.e., they are not 'well below' the guidance value, as proposed here), especially given that no effects were observed at 375(males)/390 (females) mg/kg bw/d in the 13 week study (Table 17a).	We agree that according to Haber´s rule a factor of 8 would apply for extrapolating from 13 to 104 weeks. However the factor of 2 was considered since it is mentioned in the REACH guidance R8 for the assessment factor for extrapolating from sub-chronic to chronic exposure. This is supported by literature indicating that up to 190 respective NOAEL ratios have a geometric mean between 1.5 to 2.3., depending on the analysis (Schneider et al 2006. Reg. Tox. Pharm. 44/2, 172-81 and Bokkers BG, Slob W. 2005 Toxicological Sciences 85, 1033-1040).	Under CLP, the extrapolated guidance value for an oral 2-year study is indeed 12.5 mg/kg bw/d.
		Indeed, the assessment of repeated dose toxicity is done using both long and short term studies; however, there does not appear to have been any calculations made to adjust the dose values in the long term studies (i.e., using Haber's rule) so that they can be compared correctly to the classification criteria.	In chapter 4.8.2. this is explained as follows: *"The LOAEL in the 2-year rat study at 26 mg/kg bw day (liver histopathology effects) and in the 2-year mouse study at 10 mg/kg bw day (kidney histopathology effects) are well below 100 mg/kg bw day, also if multiplied by 2 for accounting the longer*	

Date	Country/ Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
			exposure duration."	
		p45. Section 4.8.2 Although the thyroid is identified as an unequivocal target organ in the rat (p43 and p49), a mechanism is discussed on p50-52 which suggests that the effects seen in the thyroid are secondary to the effects seen in the liver. The proposed classification is therefore STOT RE 2 liver (and kidney), with no classification for thyroid effects. However, liver effects are also seen in mice and dogs, but without any associated thyroid effects – is it known why? The proposed mechanism can only explain the thyroid effects in male rats. Given that the thyroid is identified as one of the tissues with the highest concentration of etofenprox after dosing (see the toxicokinetic study on p25), can a direct effect of etofenprox on the thyroid in rats be totally excluded?	Thyroid effects were observed only in the rat and mechanistic data support a rat specific MoA: hepatic enzyme induction eliminating circulating T4 leads to increased TSH and consequent stimulation of thyroid cells. The effect is considered less or not relevant to humans, since the human plasma levels of T4 are much higher and the turn over slower. This leads to a much more stable T4 concentration in humans and therefore T4 reduction will lead to a comparatively reduced positive feedback on TSH synthesis and hypertrophy of thyroid follicular cells. Therefore it was not considered for STOT RE discussion.	

ATTACHMENTS RECEIVED:

1. Manufacturer comments on Annex XV dossier proposing CLH for Etofenprox.zip Submitted by Switzerland / Company-Manufacturer LKC Switzerland Ltd. *Attachment text is identical as in the table.*