ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Substance name: Epoxiconazole
CAS number: 133855-98-8
EC number: 406-850-2

General comments

Date	Submitted by	Organisation/ MSCA	Comment	Response	Rapporteur Comments
07/04/2009	**Andrea Caitens**	**UK/**	The proposal to classify epoxiconazole with Category 2 for reproductive toxicity (developmental toxicity; R61) does not consider the available data in a way that links clearly to the classification criteria. Of particular note, the results of the new studies regarding endocrine disruption potential have not been discussed in the context of the criteria for Category 2 or 3 in order to show which classification is most appropriate. The proposal does not contain any rationale for the classification that is proposed and, as it stands, appears unjustified.	Classification criteria The criteria states that "developmental toxicity, is taken in its widest sense to include **any effect interfering with normal development** - -"(Directive 67/548/EEC, Annex VI, 4.2.3.3) and very similar wording in the CLP regulation 1272/2008, Annex I, 3.7.1.4 " developmental toxicity includes, in its widest sense, **any effect which interferes with normal development of the conceptus**,- -" The distinction between category 2 and 3 is dependant on how clear and convincing the test results are. In the case with epoxiconazole there are many studies with different species with support from *in vitro* assays that overall give a clear evidence of adverse effects. A justification for the proposal can be found under Conclusion on page 72. The ability of a substance to cause a total imbalance of the hormones that are essential for a normal progeny by disruption of the endocrine system, in the case for epoxiconazole by inhibiting aromatase, that converts testosterone to estradiol, must fall into that category of	The RAC Rapporteur is in agreement with RCOM that classification should not be based on the mechanism *per se* but on the effects that are observed and could be due to disruption. In relationship with endocrine disrupting activities the action of Epoxiconazole on aromatase has been demonstrated *in vitro*. However, it is not clear whether it is linked to adverse developmental effects *in vivo*. The studies of Taxvig 2007 and 2008 investigate effects on sperm quality, hormonal levels and on anogenital distance (AGD). Together these studies failed to identify an effect on sperm quality or a significant reproducible effect on AGD. Variations of hormonal levels were seen in both studies but only an increase in maternal testosterone level was consistently identified and no significant effect on hormonal levels was seen in the offspring. Many uncertainties therefore remain on the potential nature and severity of *in vivo* developmental effects resulting from expression of aromatase inhibition. The RAC rapporteur supports the conclusion

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				effects that interfere with the normal development. Thus, it is fully in line with the criteria to classify for the adverse effects caused by endocrine disruption. This has already been done for other endocrine disrupting substances also for other conazoles with this intrinsic property. The classification is not based on the mechanism *per se* but the effects that are caused by this disruption. The mechanism behind a toxic effect to reproduction is not required for classification. In fact, it is unknown in most cases. When such information is available though, it can support a classification if the mechanism is known to occur also in man. This is the case with the inhibition of steroid synthesis induced by epoxiconazole. Therefore, the relevance for humans is very strong. Also, other effects not regularly tested for such as low dose effects or functional or behavioural effects manifested after puberty can be suspected. Diethylstilbestrol (DES) can serve as an example. Pregnant women were treated with DES to prevent miscarriages and they gave birth to apparent normal babies. The children developed normally until the onset of puberty when the girl developed cervical and rare vaginal cancer. Both boys and girl had problems related to reproduction and in some cases the sexual preferences was changed.	of the evaluation under Directive 91/414/EC that further studies addressing the potential endocrine disrupting properties of Epoxiconazole were necessary and therefore considers that the data available at this date on potential developmental endocrine disruptive effects are not sufficient to justify a revision of classification. The RAC adopted this conclusion on developmental endocrine disruptive effects of epoxiconazole. However, RAC concluded that induction of post-implantation loss in particular due to late resorptions and induction of cleft palate warrant revision of classification in cat. 2; R61.
			The UK intends to submit a classification and labelling proposal for another pesticide	Yes, perhaps they do.	

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			shortly. This shows effects similar to those observed in the Taxvig C et al 2007 study with epoxiconazole (e.g. alters progesterone levels in treated dams and causes dystocia). To ensure consistency, the RAC may find it beneficial to consider the 2 substances together.		
			The report provides information on some other hazards e.g. mutagenicity and carcinogenicity. It is not clear why the report includes such information as no related amendments to the classification are proposed. Are these to be considered by ECHA?	Studies on other endpoints than those concerning reproductive toxicity have been included because they give information of value for the general toxicity in relation to or support of the findings in reproductive toxicity tests. The cancer test for example shows tumours in endocrine organs ovary and the adrenals. The acute toxicity or repeated dose test could give information worthwhile for an estimation of maternal toxicity.	Discussions and recommendations of the RAC have focused on the potential revision of classification for developmental toxicity. Additional data are useful to understand the toxicological profile of Epoxiconazole.
			Page 74 The statement that 'new data show epoxiconazole to be a potent endocrine disrupter' has not been supported in the human health hazard assessment section. Specifically, please clarify what evidence and what criteria have been used to establish endocrine disrupting potency	Page 74 The definitions as endocrine disrupter is based on the definition: A substance or mixture that alters functions(s) of the endocrine system causing adverse effects in an intact organism, or its progeny, or (sub)populations In *in vitro* assays using different cell systems epoxiconazole is considered to be a potent aromatase inhibitor (Wuttke 1995 and 2001) where concentration and the percent of inhibition is valuated against positive control, another conazole Vorozole (10^{-7} M). In rat granulose cells	The Rapporteur is not aware of specific criteria or of a regulatory definition of what is an endocrine disruptor or a potent endocrine disruptor. It should be however noted that endocrine disruption is not identified in itself as an hazardous properties in the context of classification, which is based on induction of adverse effects. Mechanistic aspects related to endocrine disruption should be used in the weight of evidence approach only as supportive evidence to identified adverse effects.

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				the inhibition of 0.1µmol/L of epoxiconazole reduced the production of estradiol with appr. 70 %. This kind of inhibition also occurs *in vivo* in rats dosed with 1500-3000 ppm epoxiconazole in the diet, as shown by Mellert 1992 and 1999. To our knowledge there are no specific criteria or official definition of what is considered as potent endocrine disrupter. However, when a substance like epoxiconazole can cause many types of endocrine effects at relatively low doses, *in vitro* as well as *in vivo*, in more than one species, in different studies from different laboratories and when the effects are very relevant to man, it is justified to consider the substance as a potent endocrine disrupter.	
07/04/2009	**Stefan Stinchcombe**	**Germany/ BSAF SE**	BASF is hereby submitting a detailed position paper to address the toxicological evaluation and classification and labelling of Epoxiconazole proposed by Sweden in the Annex XV dossier. This position paper plus supporting documentation is provided in the attached zip-file. Overall, BASF wishes to make the following general comments: 1) A harmonised classification and labelling of epoxiconazole already exists. With their submission of an Annex XV Dossier "PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING - Substance: Epoxiconazole" on 25 July 2008 (revised December 8), Sweden has initiated the 4th round of expert discussions on	This is more a question of the procedure but the reason behind our wish to re-open the discussion is that the classification of epoxiconazole accepted and published in ATP28 was more correct than the one in ATP29. Studies performed after that time period has been in support of this view. In the summary record from the TC C&L meeting in May 2007 it is said that "In case a Member State considers that, on the basis of the new data on the endocrine disruption, there is a need to re-classify epoxiconazole, they should send a proposal in Annex XV format to ECHA." This Annex XV dossier has now been	1) and 2) Overall, 3 new studies were published after revision of Epoxiconazole classification in the ATP29: two of them - Taxvig 2007 and Birkhøj Kjaerstad 2007 - were submitted to TC C&L in 2007 and it was concluded by TC C&L that they do not justify re-opening of the

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			classification and labelling of epoxiconazole. The current harmonised classification and labelling of epoxiconazole decision has been published in Commission Directive 2004/73/EC (the 29th ATP to Directive 67/548/EEC), and is based on intensive consideration of all relevant data by ECB's Technical Committee on Classification and Labelling, subgroup Pesticides and Biocides. It is not clear why resources were put into the submission of an Annex XV Dossier on epoxiconazole, while on the other hand numerous compounds have never been put through the process of classification and labelling harmonisation. 2) Two publications from 2007 claimed in the Annex XV dossier to be "new", have actually already been provided to all MS Experts of the ECB Technical Committee for Classification and Labelling of Dangerous Substances. In October 2007, ECB requested Member State Experts to review the new publications before giving a final opinion on the possible re-opening classification discussion of epoxiconazole. On the basis of these publications and in consideration of the Swedish arguments, a clear majority of the Member State Experts did not support a re-discussion of the classification and labelling of Epoxiconazole. In parallel, the publications were also assessed by the Rapporteur Member State Germany in the process of the EU authorisation of epoxiconazole as active ingredient under Directive 91/414/EEC. Also Germany concluded that	submitted. A response to this BASF document will be prepared separately.	discussion as too few MS were considering that it brings sufficient new data to support re-opening. The third study – Taxvig 2008 – is a repetition of one part of Taxvig 2007. This study is therefore not considered to bring information on any additional endpoints not addressed in previous studies and evaluations. In the view of these elements, the Rapporteur considers that the recommendation of the TC C&L not to re-open discussion on developmental classification of Epoxiconazole should be followed. RAC however decided during RAC 8 that the three new published studies provide new evidence of developmental toxicity of Epoxiconazole that were not taken into account in the classification of the 29° ATP and an in-depth re-evaluation of developmental toxicity has to be performed as a classification should be based on a weight of evidence analysis of the whole database.

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			the data do not warrant a change of classification of epoxiconazole. Further arguments are presented in the attached BASF position paper "Epoxiconazole (BAS 480 F): BASF comments on the Annex XV Dossier prepared by Sweden with a proposal for harmonization of the classification and labelling of epoxiconazole in the EU", BASF DocID 2009/1050275.		

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08/04/2009	**Caoimhe Wright**	**Ireland/** Pesticide Control Service, Department of Agriculture, Fisheries & Food	Re: Re-discussion of classification and labelling of Epoxiconazole 1. General comments Sweden has submitted a comprehensive Annex XV dossier to ECHA asking for classification and labelling to be harmonised across the European Union (Press release ECHA/PR/09/02 (Feb 2009). Sweden proposes that Epoxiconazole be reclassified as Repr. Cat. 2; R61, according to 67/548 Criteria. Epoxiconazole is classified according to the Commission Directive 67/548 (29th ATP to Directive 67/458/EEC) and is in Annex I of that Directive with the following classification: Þ Carc. Cat. 3 R40 Þ Repr. Cat 3. R62 Þ Repr. Cat 3. R63 2. Irelands position After consideration of all the documentation 1-4 and an independent peer review of the original DAR 5, addendum to the DAR 6, (EFSA scientific report 2008) and ECB meeting reports and follow up written procedures 7, Ireland does not support re-opening of the discussion to reclassify Epoxiconazole. The justifications not to re-open the	Epoxiconazole was already classified as Repr. Cat. 2 in ATP28.	See previous comment. The Rapporteur also notes that the revision of the developmental classification after ATP28 was made on the request of Industry that submitted at least one new study (assumed by the Rapporteur to be Schneider 2002) according to the Summary records of TC C&L meeting of January 2003. Based on the elements available in 2003, a majority of Member States (6 for cat. 3, 3 for cat. 2) supported downgrading of Epoxiconazole from Repr. Cat. 2 to Repr. Cat. 3.

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			discussion on classification and labelling of Epoxiconazole are as follows: · In January 2003, the Technical Committee C & L Health Pesticides Expert Group changed the classification from Repr. Cat. 2; R 62 to Repr. Cat. 3; R62 after detailed consideration and discussion of all the relevant toxicological studies. · In May 2004 in Riga the final report of the Working Group on maternal toxicity was made available to the TC C&L Health Members State experts. · The current harmonised classification and labelling of Epoxiconazole decision was published in Commission Directive 2004/73/EC (29th ATP to Directive 67/458/EEC) and was based on intensive consideration of all relevant data by the ECBs Technical committee on Classification and Labelling, subgroup Pesticides and Biocides. · In March 2007, Sweden submitted a proposal to ECB to change the classification of Epoxiconazole from Repr. Cat 3. R62 to Repr. Cat. 2; R61. As the documents were not disseminated to MS for review before the May 2007 meeting, the Chair at the meeting asked MS "to react in the Follow-Up written procedure if they wanted to reopen the discussion on Epoxiconazole. · In October 2007, during the follow up written procedure Sweden submitted two		

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			new publications to the ECB (3207a4_S_Epoxiconazole.pdf and 3207a5_S_Epoxiconazole.pdf are references 3 and 4 in Annex XV dossier). The study authors are Taxvig et al., 2007 6 and Birkhoj et al., 2007 7. The ECB disseminated these papers to all MS by email for peer review. In addition, it is noted that, these two new papers had been reviewed and evaluated by the RMS Germany during the EU authorisation process under Directive 91/414 and the evaluation by Germany is included in the DAR (February 2008) which can be downloaded from the EFSA website; http://www.efsa.europa.eu/cs/BlobServer/PRAPER_Conclusion/Epoxiconazole_addendum_final.pdf?ssbinary=true. · In the same follow up period in September 2007 (Document follow up III, Revision 1) "only 3 member states (out of 27) supported re-opening the reproductive toxicity discussion of Epoxiconazole". Furthermore the ECB requested the MS to give their opinion on this issue and concluded, " if there were no further support by other MS experts the discussion will no be re-opened". The issue was not re-opened despite the deadline of r the comment being extended. · On the 24th October 2007 during the same follow up written procedure (Document Follow up Procedure IV) it was determined there was no new data on the reproductive toxicity issue regarding Epoxiconazole and		

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			Ireland and Denmark did not agree re-open the discussion on reclassification. 3. Conclusion Ireland is of the opinion that all data including the two studies by Taxvig et al., 2007 3 and Birkhoj et al., 2007 4 submitted by Sweden in 2007 have been thoroughly evaluated by the RMS Germany and undergone extensive peer review by MS under both Directives 91/414 and Directive 67/548. Ireland has reviewed Sweden's Annex XV and has not found any new data or studies submitted to support a scientific justification to re-open the discussion on classification and labelling of Epoxiconazole at this time. 4. References 1. Annex XV Dossier – Harmonisation of C&L format, Proposal for Harmonised Classification and labelling, Sweden 2009. 2. Stinchcombe, S., Epoxiconazole (BAS 480 F), BASF comments on the Annex XV Dossier prepared by Sweden with a proposal for harmonisation of the classification and labelling of Epoxiconazole in the EU, BASF, The Chemical Company, Product Safety, Regulations, Toxicology and Ecology, April 2009.		

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			3. Taxvig et al., Endocrine disrupting activities in vivo of the fungicides tebuconazole and epiconazole, Toxicol Sci, 100, 464-473, 2007. 4. Birkhoj, K.M., Ruan Anderson, H., Taxvig, C., Hass, U., Axelstad, M., Metzdorff, S., Vinggaard, A.M., Effects of azole fungicides on the function of sex and thyroid hormones, Pesticide Research No 111, Danish Environmental Protection Agency, 2007. 5. Epoxiconazole DAR, RMS Germany, 26th March 2008 http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902024675.htm 6. Addendum to Epoxiconazole DAR, RMS Germany, 26th March 2008 http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902024675.htm 7. ECB Meetings and Follow Up Reports and Procedures, http://ecb.jrc.ec.europa.eu/classification-labelling/MEETINGS/public.htm		
09/04/2009	**Karl Otto Westphalen**	**Germany/ BASF SE**	BASF Comment on Sweden's Annex XV dossier for Epoxiconazole Ref.-No.: 1efe42cb-8009-4c45-a26a-		-

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			3c9417cbb6de On Tuesday, 07. April 2009 we have submitted our comments and uploaded a corresponding zip file with attachments to this website. In order to ensure that attachments are available to EChA we are sending them once again today, April 09, 2009. Kind regards Karl-Otto Westphalen		

Carcinogenicity

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07/04/2009	**Andrea Caitens**	**UK/**	Pages 16 – 18 There is no proposal to amend the existing classification for carcinogenicity so it is not clear why information relating to this endpoint has been included in the proposal	See explanation above to the comments from UK.	Discussions and recommendations of the RAC have focused on the potential revision of classification for developmental toxicity. Additional data are useful to understand the toxicological profile of Epoxiconazole.
09/04/009	**Jan Averbeck**	**Germany**	Page 16-18 Epoxiconazole is currently classified as a carcinogenic substance category 3 (Carc. Cat. 3; R 40) in Annex I of Directive 67/548/EEC. No change in the current classification is proposed.	See explanation above to the comments from UK.	Same comment as above.

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Mutagenicity

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07/04/2009	**Andrea Caitens**	**UK/**	Pages 14-15 There is no proposal to amend the existing classification for mutagenicity so it is not clear why information relating to this endpoint has been included in the proposal	See explanation above to the comments from UK.	Same comment as above.
09/04/009	**Jan Averbeck**	**Germany**	Page 14-15 Epoxiconazole has no genotoxic potential. No classification is proposed	See explanation above to the comments from UK.	Same comment as above.

Toxicity to reproduction

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02/04/2009	**Christiane VLEMIN CKX**	**Belgium /** Scientific Institute of Public Health	p72-73: In January 2003 a vast majority of Member States (including Belgium) supported a classification in Repr. Cat.3 ; R63. This decision was based on the fact that a high incidence of cleft palates appears in a range finding study in rats at a dose which is severely toxic for the dams and the fact that this high incidence was not reproduced in the other studies. Epoxiconazole is clearly foetotoxic and embryotoxic (increases in post-implantation loss, resorptions stillborn pups and postnatal deaths have been observed in several studies with a concurrent decrease in liveborn fetuses/live litter size and in viability index). In addition, in the rat, it induces malformations (especially cleft palates),	Thank you for the support.	The developmental toxicity of epoxiconazole was investigated in a two-generation reproduction study (rat), a prenatal toxicity study (rat), preceded by a range-finding study, two maternal toxicity studies (rat; one without evaluation of the foetuses), a prenatal development toxicity study (rabbit), a dermal prenatal toxicity study (rat) and two additional developmental toxicity studies (rat), with special focus on endocrine disrupting effects (Taxvig *et al*., 2007 and 2008). Data showing induction of foetotoxicity and malformations by Epoxiconazole were thoroughly reviewed in 2003 by the TC C&L that concluded that a classification Repr. Cat. 3; R63 is appropriate. Indeed,

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			mainly at doses which are severely materno toxic. Even if this malformation occurs in presence of maternal toxicity it is considered to indicate a clear teratogenic potential of epoxiconazole and not a secondary effect related to maternal toxicity. This typical pattern of developmental toxicity was also observed with other triazoles and in vitro data support the hypothesis that triazole-derivatives may produce cranio-facial abnormalities. Endocrine disruptive effects have been reported in vitro in several species including man. Moreover, new studies in rats have shown that it has endocrine disrupting effects in vivo, resulting in effects on both dams and offspring (in particular female foetuses and offspring) at doses that are not or very slightly toxic to the dams. Depending on the weight put onto the most recent published studies, a classification in Repr. Cat. 2 ; R61 may be supported.		epoxiconazole is clearly foetotoxic and induces cleft palates in the rat in presence of maternal toxicity and it is considered that these effects justify a classification Repr. Cat. 3; R63 in line with previous evaluation. On endocrine disruption, no significant reproducible effect was seen on the anogenital distance. Epoxiconazole was however capable of inducing variations of hormonal levels in the dams but no significant effect on hormonal levels was seen in the offspring. Overall, many uncertainties therefore remain on the potential nature and severity of *in vivo* developmental effects resulting from effects observed *in vitro.* Besides, the review of Epoxiconazole under Directive 91/414/EEC concluded that further studies addressing the potential endocrine disrupting properties of Epoxiconazole were necessary (Directive 2008/107/EC). It is therefore considered that the data available at this date on potential endocrine disruption are not sufficient to justify a revision of classification. The TC C&L also concluded in 2007 that new studies did not justify revision of the classification. In absence of any additional significant new data, the recommendation of the TC C&L should be followed.

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					The RAC however decided during RAC 8 that the three new published studies provide new evidence of developmental toxicity of Epoxiconazole that were not taken into account in the classification of the 29° ATP and an in-depth re-evaluation of developmental toxicity has to be performed as a classification should be based on a weight of evidence analysis of the whole database. Further to the in-depth evaluation, the RAC agreed that revision of classification was not justified by potential developmental endocrine disruptive effects of epoxiconazole. Induction of post-implantation loss by epoxiconazole was confirmed by the RAC, in particular induction of late resorptions. It was observed in absence of maternal toxicity in the Taxvig studies and was therefore considered by the RAC that it cannot be secondary to non specific maternal toxic effects. It is also considered by the RAC that induction of cleft palate cannot be secondary to non specific maternal toxic effects. The RAC therefore concluded that these two effects therefore warrant revision of classification in cat. 2; R61.
06/04/2009	**Antony FASTIER**	**France / AFSSA -**	Reproductive toxicity : e.g. p.43 and p.62 conclusion on the new		

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		DIVE	studies not included in the DAR In the new in vitro study, epoxiconazole acts via several endocrine disrupting pathways in vitro. In some assays, epoxiconazole effects were lower than other azole fungicide like prochloraz. Furthermore, it is not known if these effects (for example anti-androgenic effects) are induced in vivo. In the new in vivo study, epoxiconazole was primarily fetotoxic. Therefore, only results at dose 15 mg/kg were interpretable. Epoxiconazole was capable of altering sex hormone levels in dams but not in foetuses and increasing anogenital distance in female offspring at 15 mg/kg. Epoxiconazole effects in these new studies are in accordance with the previous conclusion on epoxiconazole as a potent endocrine disruptor. More mechanistic studies are needed to address the exact mechanism behind the virilizing effects of females and to address which step in the steroid synthesis are affects. Conclusions : According to the new studies submitted,	The inhibition of aromatase results in higher levels of androgens both in males and females (Mellert 1992 and 1999). This is the most plausible explanation of the virilising of females. Also, the protective role of estrogen toward the influence from androgens is also diminished. The TC C&L group is an advisory group to	The studies Mellert 1992 and 1999 were available at the time of last Epoxiconazole classification evaluation by TC C&L in 2003 that resulted in classification in category 3. The studies by Taxvig 2007 and 2008 failed to identify a significant reproducible effect on AGD. Variations of hormonal levels were seen in both studies but only an increase in maternal testosterone level was consistently identified and no significant effect on hormonal levels was seen in the offspring. According to the Summary records of

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			there is no new evidences that the current classification should change. Provided that a consensus was reached on the classification Xn, Carc. Cat. 3 R40, Repr. Cat. 3 R62, Repr. Cat. 3 R63, our opinion is that the new studies does not warrant any change in the current classification.	the COM and a consensus decisions are therefore not required. A consensus decision on the classification of epoxiconazole was not reached.	TC C&L meeting of January 2003, recommendation to classify in cat. 3 was made based on the support of 6 MS (AT, DK, B, D, F, UK) against 3 MS for cat. 2 (IRL, FIN, S). In 2007, the decision not to reopen discussion was based on the fact that only few MS supported reopening, i.e. 4 MS were supporting (NL, N, S, HU).
07/04/2009	**Andrea Caitens**	**UK/**	Pages 19-73 Epoxiconazole has been discussed under the previous classification and labelling system at ECB and the classification for developmental effects, based on cleft palate, considered. As a result, classification with Repr. Cat. 3; R63 was agreed. This new proposal does not appear to contain any new evidence on cleft palate that would warrant further discussion or an increase in the classification to Repr. Cat. 2; R61 based on this finding. Pages 40-43 and 60-62 The proposal presents some data that were	Pages 19-73 An existing classification as Repro. Cat. 2; R61 adopted to ATP28 which was changed to Cat. 3; R63 in ATP29. Also, see the separate additional response to CLH-RCOM-BW003153-39. It is not only the incidence of cleft palate but also other developmental effects such as implantation losses, resorptions and pup morality that have to be accounted for to give a suitable classification. In the Taxvig 2007 study for instance there are very high rate of postimplantation losses, late and very late resorptions, perinatal loss and postnatal loss at a dose of 50 mg/kg bw, a dose that did not induced any maternal toxicity, measured as no change of maternal body weight gain GD7-GD21 or GD7-PND1. Pages 40-43 and 60-62	Taxvig 2007 and Taxvig 2008 also include data on developmental effects other that endocrine disruption, including post-implantation loss and resorptions. In relationship to maternal toxicity, in Taxvig 2007 maternal body weight gain GD7-PND16 of dams allowed to deliver was decreased of -12% and -27% respectively compared to controls in the 15 and 50 mg/kg groups, although not statistically significant. A loss of weight was also observed in dams of the 15 mg/kg group during PND1-PND13 (results not relevant at the highest dose based on 1 dam only). Adjusted maternal body weight of dams sacrificed for caesarean section was however not significantly affected in Taxvig 2007 and is not known in Taxvig 2008. No

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			not discussed in an organised meeting under the previous classification and labelling system at ECB (the Taxvig C et al. 2007 study and the Birkhoj Kjaerstad M. et al. 2007 study). However, these studies were presented in the written follow-up procedure to the TC C&L meeting in May 2007 (ECBI/32/07 Adds.4 and 5). As a consequence of that procedure the majority of Member States concluded that the information presented did not warrant a re-opening of the discussion on reproductive toxicity. In addition, this new proposal does not consider these data in a way that links clearly to the classification criteria for developmental toxicity. For example, the relevance of the increase in anogenital distance to the assessment of developmental toxicity is not discussed adequately. Additionally, there is no consideration of i) experimental design and ii) generalised toxicity as described in the criteria. Consequently, the proposal does not contain any rationale for the classification that is proposed and therefore appears unjustified.	Also, the *in vitro* investigations should be used to strengthen the *in vivo* results. Other relevant information should be considered. All effects in its widest sense to include any effect interfering with normal development should be taken into account 67/548/EEC Annex I 4.2.3.3 (2). This comments i) and ii) are not fully understood. If a study is of acceptable quality it will be evaluated. It is not only the conventional Guideline studies that should be considered. The generalised toxicity is always considered as a part of an evaluation.	information on maternal food consumption was available in these studies. Besides, these studies don't follow guidelines and were performed with low number of animals compared to guidelines. The numerous guideline studies showing induction of foetotoxicity and malformations by Epoxiconazole and their relationship with maternal toxicity were thoroughly reviewed in 2003 by the TC C&L that concluded that a classification Repr. Cat. 3; R63 is appropriate. The RAC however decided during RAC 8 that the three new studies provide new evidence of developmental toxicity of Epoxiconazole that were not taken into account in the classification of the 29° ATP and an in-depth re-evaluation of developmental toxicity has to be performed as a classification should be based on a weight of evidence analysis of the whole database. Further to the in-depth re-evaluation of the whole database, induction of post-implantation loss by epoxiconazole was confirmed by the RAC, in particular induction of late resorptions. During RAC 9, clarifications were provided by Ulla Hass, one of the authors of the Taxvig studies. She indicated that maternal corrected body weight was not significantly affected by treatment in

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					Taxvig 2008. Although maternal food consumption was not assessed in these studies that were not performed according to guidelines, the RAC considered that they are scientifically robust. The RAC therefore concluded that post-implantation loss cannot be considered as secondary to non specific maternal toxic effects. It is also considered by the RAC that induction of cleft palate cannot be secondary to non specific maternal toxic effects. The RAC therefore concluded that these two effects therefore warrant revision of classification in cat. 2; R61.
			Page 36 and 41 We note that there are some conflicting data in the proposal regarding progesterone levels in treated dams. Page 41 (the Taxvig C et al. 2007 study) states that there was an increase in progesterone levels (7 fold) whilst page 36 (the Schneider S.et al. 2002 study) shows that there was a decrease in progesterone levels. In the Taxvig C et al. 2007 study it states that the increased level of progesterone was associated with "the increased gestational length and the virilising [masculinisation?] effect seen in the female offspring". However, the significance of the decrease in progesterone levels is not provided in the	Pages 36 and 41 It is not only the levels of progesterone that are changed but also estradiol and androgens. Especially progesterone concentrations in plasma is increased during pregnancy, in humans 20-folld increase, followed by a sudden drop at time for labour. The time point for blood sampling is very important because the progesterone levels in the pregnant rat is dramatically changed the last few days of pregnancy with a sudden drop in concentration of at least 50 % between GD19 to GD21. Different doses have been tested 50 mg/kg bw in the Taxvig study and 180 mg/kg bw in the Schneider study which also could give a different response. The control values	Measurement of hormonal levels in females showed consistent effects on a decreased level of estradiol (Mellert 1992 and 1999, Schneider 2002, Taxvig 2008) and an increased level of testosterone (Taxvig 2007 and Taxvig 2008). Inconsistent results were observed with progesterone levels (decrease in Schneider, increase in Taxvig 2007). Besides, no significant effect on hormonal levels was seen in the offspring. The available information on hormonal levels is therefore not sufficient to justify a revision of the developmental classification of

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			conclusion to the Schneider S.et al. 2002 study. Consequently, in the absence of an explanation, the findings are unclear and suggest that classification in category 3 is appropriate	for progesterone also differ 48 compared to 198 nM in resp. study.	Epoxiconazole based on potential developmental endocrine disruptive effects. The RAC adopted this conclusion on developmental endocrine disruptive effects of epoxiconazole. However, RAC concluded at RAC 9 that induction of post-implantation loss in particular due to late resorptions and induction of cleft palate warrant revision of classification in cat. 2; R61.
07/04/2009	**Stefan** Stinchcombe	**Germany/ BSAF SE**	Please refer to the attached BASF position paper: "Epoxiconazole (BAS 480 F): BASF comments on the Annex XV Dossier prepared by Sweden with a proposal for harmonization of the classification and labelling of epoxiconazole in the EU" (BASF DocID 2009/1050275) and to supporting documentation, which are provided in the attached zip-file	The BASF position paper will be commented separately.	-
09/04/009	**Jan Averbeck**	**Germany**	The data that support an endocrine disruptive effect on anogenital distance are not convincing. In one study (Taxvig et al., 2007), an increased anogenital distance (AGD) in female rat offspring has been described and has been attributed to an effect of epoxiconazole on maternal progesterone levels which were increased at the end of pregnancy. These findings are in contrast to the data of Schneider S. et al. 2002, TOX2002-2288, Reg. No. 2002/1012810 who found a significant decrease of maternal progesterone levels during exposure. Moreover, the data on AGD increase in	The effects on AGD probably depend on the balance between estrogens and androgens. The androgens give a larger AGD but the oestrogens are protective of such effects.	See above comment on hormonal changes. In Taxwig 2007, AGD was increased in both female foetuses at GD 21 and in newborn female offspring but it was not repeated in Taxwig 2008, in which a non-significant decrease in AGD in female foetuses was observed. There were indications of an effect on AGD in males, but in both studies the effects were not consistent between foetuses and pups, or between the AGD and the anogenital index (i.e. the anogenital distance adjusted for weight

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			females are questionable because in another study by these authors (Taxvig et al., 2008) no increase in female offspring AGD was found when an epoxiconazole dose of 50 mg/kg bw/d was given to the same strain of rats from GD 7 to GD 21 (e.g. including the programming window for masculinization). Moreover, considering the control data from this second study as well as from the first, the variability of the measure seems to be high as the difference between the two control groups on GD 21 is larger than any difference beween treated and control groups within any of the individual studies.	In the Taxvig 2007 study the control data of the AGD in males are for the offspring data 3.41 ±0.2 and from the GD21 males 3.39±0.3 and for females 1.72±0.1 and 1.65±0.1 mm. In the Taxvig 2008 study male AGD is 3.76 ±0.08 and for females 2.12± 0.03 m The control within the study must be the one to use for a comparison. That is the best approximation of that the experimental conditions are identical. That is why internal controls always are included in studies.	differences) and the effect was not dose-related in Taxwig 2007 (only one dose in Taxvig 2008). Overall, no significant reproducible effect on anogenital distance was therefore seen.
			The substance has been discussed in the Technical Committee (TC C&L) under Dir. 67/548/EEC and was included in the 28th ATP as Repro Cat. 2; R61. This classification was revised in the 29th ATP in 2004 where additional data on developmental toxicity and maternal toxicity were evaluated. Based on this information, the classification of epoxiconazole was changed to Repr. Cat 3; R63 in Annex I to Dir. 67/548/EEC. It should be thoroughly reflected before reopening discussions on classification and labeling recently published in 29th	The view on how to consider maternal toxicity with regard to reproductive effects has been modified since this decision. Examples of that is the Expert guidance document ECBI/30/04 from 2004 (one so called yellow paper which was accepted by the TC C&L group as a guidance on maternal toxicity) and the feed restriction study by Fleeman 2005.	It should be noted that modification in the way to consider maternal toxicity was raised by Sweden during consultation of the TC C&L in 2007 on potential reopening of developmental classification (ECB documents 3207-I_S_epoxiconazole.doc=request for revision of classification and 3207-II_S_epoxiconazole.doc=Fleeman 2005). Considering these elements, it was concluded by TC C&L that re-opening of the discussion is not justified. See also above response to comments

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			ATP. Thus, based only on the new studies from Denmark, the current classification should not be questioned. If RAC decides to reopen these issues then all studies available related to the endpoint in question should be taken into account. Additional References C. Taxvig, A. M. Vinggaard, U. Hass, M. Axelstad, S. Metzdorff, C. Nellemann Endocrine-disrupting properties in vivo of widely used azole fungicides. International Journal of Andrology 31, 170-177, 2008		7 on foetotoxicity and maternal toxicity. The study of Taxvig 2008 has been included by the Rapporteur in the Background Document and considered by the RAC in the evaluation of the whole database.
09/04/2009	**Zsuzsanna Kiss**	**Hungary/**	Point 5.9.1., page 43- The critical effect of epoxiconazole is reprotoxicity and carcinogeneicity. The results from the new in vitro study (Birkhøj Kjjærstad, M. et al. (2007)) and the new developmental study in rats (Taxvig, Camilla et al. (2007)) confirm that epoxiconazole has endocrine disrupting properties. Although, in vitro studies demonstrate only the way(s) how epoxiconazole can act as an endocrine disruptor investigating together with the animal studies they suggests that epoxiconazole has more severe developmental (i.e. foetotoxic) effects as it was marked previously	This comment seems to have been partly lost and it is not possible to give an answer.	-

Date	Submitted by	Organisation/ MSCA	Comment	Response	Rapporteur Comments

Respiratory sensitisation

Date	Submitted by	Organisation/ MSCA	Comment	Response

Other hazards and endpoints

Date	Submitted by	Organisation/ MSCA	Comment	Response	Rapporteur Comments
07/04/2009	**Andrea Caitens**	**UK/**	Pages 9-10 and 11-13 The report also contains information relating to acute toxicity and repeated dose toxicity, but there is no proposal to amend the existing classification for these endpoints. Consequently, it is not clear why this information has been included in the proposal.	See explanation to the comments from UK.	Discussions and recommendations of the RAC have focused on the potential revision of classification for developmental toxicity. Additional data are useful to understand the toxicological profile of Epoxiconazole.

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COMMENTS RECEIVED

FROM MSCAS

IRELAND: Re-discussion of classification and labelling of Epoxiconazole

BELGIUM: Epoxiconazole – ANNEX XV Dossier – Harmonisation of C & L – Submitted by Sweden - Position of ISP Division Toxicology

SWEDEN: SE comment on the inclusion of the active substance epoxiconazole on Annex I to the Directive 91/414/EEC and classification and labelling under the Directive 67/548/EEC.

ECB DOCUMENTS

Email from Ingrid Langezaal 17.10.2007.

DOCUMENT ECBI/32/07 Add. 1. Reproductive toxicity (Annex IIA 5.6). Epoxiconazole - summary table reproduction and prenatal toxicity.

Document ECBI/32/07 Add. 2. Comments of SE on the draft assessment report on epoxiconazole (9.12.2005)

Document Follow-up V of the meeting of the Technical Committee on Classification and Labelling in Arona, 15-16 May 2007. Ispra, 29 May 2008.

SCIENTIFIC PUBLICATIONS:

C. Taxvig, A. M. Vinggaard, U. Hass, M. Axelstad, S. Metzdorff and C. Nellemann (2008). Endocrine-disrupting properties in vivo of widely used azole fungicides, International Journal of Andrology 31, 170–177.

Fleeman TL, Cappon GD, Chapin RE, Hurtt ME. The effects of feed restriction during organogenesis on embryo-fetal development in the rat. Birth Defects Res B Dev Reprod Toxicol. 2005 Oct;74(5):442-9.

MANUSCRIPTS:

C Taxvig, U Hass, M Axelstad, M Dalgaard, J Boberg, H R Andersen and A M Vinggaard. Endocrine disrupting activities *in vivo* of the fungicides Tebuconazole and epoxiconazole. ToxSci Advance Access published September 4, 2007

REPORTS:

Effects of azole fungicides on the function of sex and thyroid hormones. By Mia Birkhøj Kjærstad and Helle Raun Andersen University of Southern Denmark, Institute of Public Health, Research Unit of Environmental Medicine Camilla Taxvig, Ulla Hass, Marta Axelstad, Stine Metzdorff and Anne Marie Vinggaard Technical University of Denmark, the National Food Institute, Department of Toxicology and Risk Assessment Pesticides Research ·No. 111 2007.

BASF DOCUMENTS:

Epoxiconazole. (BAS 480 F): BASF comments on the Annex XV Dossier prepared by Sweden with a proposal for harmonization of the classification and labelling of epoxiconazole in the EU.

Epoxiconazole. (BAS 480 F): BASF comment on Sweden's proposal To re-discuss the classification of Epoxiconazole.

Epoxiconazole. (BAS 480 F): BASF position paper on the publication Taxvig C. et al. (2007): *"Endocrine disrupting activities in vivo of the fungicides tebuconazole and epoxiconazole"* (Toxicol. Sci., 100, 464-473).