Committee for Risk Assessment

RAC

Annex 2

to the RAC Opinion

on toxicity to reproduction of

Epoxiconazole

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Adopted

28 November 2012

Committee for Risk Assessment
(RAC)

Opinion

on certain scientific study plans
in relation to epoxiconazole

ECHA/RAC/ A77-O-0000001412-86-02/F

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11 March 2011

Helsinki, 11 March 2011
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Opinion on certain scientific study plans in relation to epoxiconazole

Pursuant to Article 77(3)(c) of Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (the REACH Regulation),

the Committee for Risk Assessment (RAC) has adopted an opinion on whether the already performed, currently ongoing, or planned studies could be relevant for deciding on the appropriate harmonised classification of epoxiconazole (CAS No. 133855-98-8; EC No. 406-850-2) as toxic for reproduction Cat. 1B, according to the CLP Regulation.

The studies referred to above are the six studies that are listed on page 6 of the RAC opinion on epoxiconazole of 17 March 2010 (Annex 1) and that have been discussed with Regulatory Authorities under the approval regime of Directive 91/414/EEC. For each of these studies, study plans have been provided by the Commission and these should be the basis for the RAC opinion. These six study plans are hereafter referred to as the 'reference documents' and are listed in Annex 2.

I PROCEDURE FOR ADOPTION OF THE OPINION

Following a request from the European Commission (Annex 3), in the mandate of 17 January 2011 attached as Annex 4, the Executive Director of ECHA asked RAC to review the reference documents and provide an opinion on whether these studies could be relevant for deciding on the appropriate harmonised classification of epoxiconazole as toxic for reproduction Cat. 1B.

RAC appointed Annick Pichard as rapporteur on 28 October 2010 at RAC-13. The rapporteur carried out an adequacy check of the information provided on 11 January 2011 and confirmed that for five of the six studies there was sufficient information to form an opinion. For one of the studies, data was absent from the study protocol provided from the Commission and in turn from BASF.

Representatives from the European Crop Protection Association (ECPA) accompanied by an expert from BASF were present and contributed to the discussion of RAC on this opinion.

The RAC opinion was adopted on 11 March 2011. It complements the RAC opinion of 17 March 2010 in relation to the proposal for harmonised classification and labelling of epoxiconazole. The RAC opinion was adopted by consensus.

II OPINION OF RAC

RAC has formulated its opinion on whether the reference documents could be relevant for deciding on the appropriate harmonised classification of epoxiconazole as toxic for reproduction Cat. 1B. The opinion was based upon the information referred to in the mandate i.e. the reference documents provided by the Commission.

Based on all available data and the weight of evidence on the impact of epoxiconazole toxicity, RAC considered in its opinion of 17 March 2010 that epoxiconazole should be classified as Reprotoxic category 1B (Regulation EC No. 1272/2008) and Reprotoxic Category 2 (Directive 67/548/EEC). Two main adverse effects of epoxiconazole on development were identified and considered as critical for the classification decision:

- Post implantation loss and resorptions
- Malformations as cleft palates

After examination of the reference documents, the Committee considers that these additional studies are relevant with respect to one of the questions raised by RAC (late resorptions), whilst the potential for a teratogenic effect (cleft palates) of epoxiconazole at high dose levels (exposure) may remain unexplained**.**

Therefore, and taking into account the conclusion of the examination of the reference documents, the proposal for a harmonised classification and labelling of epoxiconazole as Reprotoxic category 1B (CLP) and Reprotoxic Category 2 (Directive 67/548) seems unlikely to be modified by the result of the studies referred to therein.

RAC has been informed that further studies concerning the cleft palate effect are ongoing. However, RAC did not look at them or the study plans because they were not part of the Commission's request dated 10 December 2010.

III SCIENTIFIC GROUNDS FOR THE OPINION

Overview of the scientific evidence

- **Conclusions in the RAC opinion of 17 March 2010**

Based on all available data and the weight of evidence on the impact of epoxiconazole toxicity, RAC considered in its opinion that epoxiconazole should be classified as Reprotoxic category 1B (CLP) and Reprotoxic Category 2 (Directive 67/548).

Two main adverse effects of epoxiconazole on development were identified and considered as critical for the classification decision:

- Post implantation loss and resorptions
- Malformations as cleft palates

- **Assessment of the endpoints to be addressed in the study protocols provided for the BASF studies.**

BASF has provided 6 protocols designed to clarify the mechanism of action leading to embryo- and foetal mortality during pregnancy as well as the occurrence of malformations (cleft palates) in rats.

Additional studies were conducted and are planned in the guinea pig to verify whether this mechanism of action is species-specific.

The proposed additional BASF studies are:

- A modified prenatal development toxicity study in Wistar rats by the oral route (gavage)
- A modified prenatal developmental toxicity study in Wistar rats with co-adminstration of estradiol cyclopentyl propionate by the oral route (gavage)
- A kinetic study in pregnant Wistar rats by the oral route (gavage)
- A modified maternal toxicity study in guinea pigs by the oral route (gavage)
- A modified prenatal developmental toxicity study in guinea pigs by the oral route (gavage)
- A study for effects on pre- and postnatal development, including maternal function in guinea pigs by the oral route (gavage).

It should be noted that the draft protocol for the pre- and postnatal developmental study in guinea pigs cannot be fully addressed as the submitted protocol only contains limited information and many key elements are missing: e.g. the dose levels and rationale for their choice. In addition, there are a number of unclear definitions of parameters to be assessed on pups.

Regarding the other study protocols, they are adequately presented and are consistent with the guidelines in force. A summary evaluation is presented below:

The rat protocols are clearly designed to only assess the role of the hormonal dysregulation (namely oestradiol deficit) on the embryo- and foetomortality in comparison with the Taxwig et al publication (1). These protocols are not designed to better explore whether the compound is teratogenic, i.e., induces cleft palates as described at high dose levels (180 mg/kg) in the Hellwig and Hildebrand report in 1989 (BASF report) or other types of malformations as reported in the Schneider study in 2002 (BASF report). In addition, signs of alert for teratogenic potential (such as presence of cervical ribs as mentioned in previous BASF reports) are not assessed at the proposed dose levels, although these effects were observed within the same range of doses in the previous BASF studies.

The specific kinetic study in rats would allow a better determination of the maternal internal exposure leading to hormonal dysregulation and therefore a better evaluation of the risk for occurrence of late resorptions and/or malformations. In addition, it would have been useful to verify the placental transfer (through measurement of the foetal or amniotic fluid concentrations) to support the various hypothesis related to the teratogenic potential (see below).

Two guinea pig protocols are designed to explore the potential adverse effects (embryo/foetotoxic effects and the teratogenic potential) of epoxiconazole on the embryo/foetal development of the guinea pig when orally administered by gavage from the beginning of organogenesis to the end of pregnancy in a second rodent species. Assessment of the maternal toxicity, homeostasis, general toxicity and potential variations in the hormonal balance are as well developed as in the rat studies. Assessment of foetal defects includes external, visceral and skeletal examination and therefore would allow detection of foetal variations and malformations. The rationale for the species selection and for choice of dose levels, especially in the modified prenatal developmental toxicity study, should have been better detailed. A clear rationale for species selection is needed to support the assumption that hormonal regulation during pregnancy in the guinea pig differs from the rat and that, therefore, the embryo/foetomortality found in the latter might be species specific. Also, a clear rationale for assuming that guinea pig is more similar to humans than the rats is needed. The absence of a kinetic study performed in parallel would allow neither the determination of the maternal internal exposure leading to hormonal dysregulation nor a comparison of the maternal exposures with those obtained in the specific rat study. An evaluation of the placental transfer would have been useful as well.

Eventually, since the guinea pig is an uncommon species used for this type of studies (use almost limited to mechanistic investigations), the absence or, at best, the limited amount of historical data on foetal spontaneous defects in this species and strain at the testing site will make the interpretation of results more difficult if there is a low incidence of foetal defects.

In conclusion, all these studies, in both species, focused on addressing the issue of the embryo/foetomortality seen in rats at dose levels affecting the maternal hormonal regulation. These studies are also designed to demonstrate that the embryo/foetomortality may be species-specific and therefore not relevant for humans. However, lack of relevance for humans is not shown as such if guinea pig studies should not show embryo/foetomortality because there is no clear rationale for assuming that guinea pig are more similar to humans that rats.

The mechanisms potentially implied in the occurrence of teratogenesis of azole derivatives at high dose levels in laboratory animals and in humans (e.g. with fluconazole) are suggested .These include inhibition of embryonic CYP 26, dysregulation of the foetal retinoic acid concentration, cholesterol synthesis pathway, Cyp51 etc…These mechanisms may be different from or complementary to those inducing the *in utero* mortality , however, this is not explored here in either test species

- **Overall conclusion on the relevance of the expected results in terms of the classification of epoxiconaloze as toxic for reproduction Cat. 1B[1].**

Therefore, even in a best case scenario assuming that the results may provide information on the mechanisms for the observed embryo/foetomortality, these BASF additional studies may address only partly one of the concerns raised by the RAC (late resorptions).

[1] This justification is based on the assessment of the information expected to be produced, taking into account the endpoints to be measured in the studies according to their protocols. The information provided on some available results has been only used as additional information whenever relevant, as the assessment of these preliminary results is not part of the RAC mandate.

Furthermore, depending on what mechanism(s) of action that is (are) identified, the data may, or may not decrease the concerns for human relevance of the late resorptions. However, the potential for a teratogenic effect (cleft palates) of epoxiconazole at high dose levels (exposure) may remain unexplained. Even if the additional studies show that the post implantation losses were considered not relevant for humans (based on mode of action information and consideration on interspecies differences) at the moment there remains sufficient reason on account of the cleft palate considerations for a 1B classification.

Therefore after the examination of the reference documents, RAC considers that the proposal for a harmonised classification and labelling of epoxiconazole seems unlikely to be modified by the results of the studies when available.

ANNEXES

Annex 1	RAC Opinion of 17 March 2010 on a dossier proposing harmonised classification and labelling at Community level for epoxiconazole.
Annex 2	List of the study plans for the six studies referred to as the 'reference documents'.
Annex 3	The request from the Commission to ECHA (ENV D3/SB/fb/Ares (2010) 929698).
Annex 4	Request from the Executive Director of ECHA to RAC (I(2011)0005 of 17 January 2011) – 'the mandate'.

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