Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

etridiazole

EC number: 219-991-8
CAS number: 2593-15-9

CLH-O-0000002504-80-02/A2

Adopted

4 June 2013

ANNEX 1 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON ETRIDIAZOLE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

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

Substance name: Etridiazole
EC number: 219-991-8
CAS number: 2593-15-9

General comments

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC response to comment
13/04/ 2012	Belgium / MSCA	We support the classification for acute oral toxicity category 4 (H302), since the LD50 (945 mg/L) in female rat falls within category 4 of the CLP Regulation criteria (300 < Category 4 ≤ 2 000 mg/kg bw). We recognize also that the minimum classification is no longer necessary. We agree that no classification is necessary for acute dermal toxicity, since the LD50 (>5000 mg/kg bw) is above the limits of criteria for the dermal route according to the CLP (1000 < Category 4 ≤ 2 000 mg/kg bw). We recognise that Etridiazole does not need to be classified for acute inhalation toxicity. Indeed, the LC50 (>5.7 mg/L) is above the limits of criteria for dusts and mists under the CLP (1.0 < Category 4 ≤ 5.0 mg/L). The classification proposal as STOT category 3 after a single dose (H335) is supported based on the local reversible effects observed in the respiratory tract. We support the classification proposal as Skin Sensitising category 1B (H317) based on a Guinea Pig Maximisation Test showing skin reactions in ≥ 30% of the animals treated with Etridiazole at an induction concentrations >1%. We agree not to propose classification regarding developmental toxicity. The severe foetal effects observed in both the rat and rabbit studies presented in the dossier occurred at levels causing excessive maternal toxicity (mortality > 10%).	Thank you for the support	Noted.

Carcinogenicity

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC response to comment
13/04/2012	Spain / MSCA	p 41. Conclusion - Carcinogenicity The Spanish CA agrees with the proposal of dossier submitter to classify etridiazole under de DSD and CLP classification criteria as Car, cat 3, R 40: Limited evidence of a carcinogenic effect, and as Carc. 2 H351: Suspected of causing cancer, based on a review of the carcinogenicity studies in rat and mouse and in the in vivo mechanistic studies in rat. Neoplastic lesions were noted in different organs in rat (Trutter, 1988): liver, thyroid, testis, mammary glands and kidney. In mouse, neoplastic lesions were observed only in the liver (Goldenthal, 2004). In most cases, their incidences were out of the historical control range for each tumour type. The mechanistic studies in rat show that etridiazol produces carcinogenesis in different organs with unknown underlying mechanism which could be relevant for humans: • In rat liver, the mechanistic studies showed that etridiazole possesses a tumour activity above a threshold, based on the induction of metabolizing hepatic enzymes, with a different biochemical profile than Phenobarbital (Tanaca, 1995), and the increase in the number and size of GST-P positive liver foci (biomarker for hapatocarcinogenicity) (Tsuda, 2003). • In rat thyroid, the mechanism of the tumour formation is unknown. Although an increase in UDP-GT was observed, the corresponding increase in the thyropropin TSH in blood or changes in thyroid hormones T3 or T4 in blood not occur (Tanaca, 1995). Therefore it should be assumed that humans are potentially susceptible. • In rat testis: interstitial cell tumours (Leyding cell tumours) were observed at all dose levels administered. However, only those observed at the hightest dose level were out of the historical control range. Since, the mechanism is not known for etridiazole, it should be assumed that humans are potentially susceptible.	Thank you for the support	Comments were taken forward to the draft opinion.

Mutagenicity- no comments received

Toxicity to reproduction

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC response to comment
13/04/ 2012	Spain / MSCA	p 51. Conclusions on classification and labelling of reproductive toxicity The Spanish CA agrees with the proposal of CLH dossier. Etridiazole does not need to be classified for its risks on reproduction and development. We agree with CLH dossier that the foetal toxicity (retarded ossification of various bones and skeletal malformations) observed in developmental studies in rat and rabbit (Wahlberg, 1982; Knickerbcker, 1979) is not considered relevant for classification.	Thank you for the support	
13/04/ 2012	Denmark / Peter Hammer Sørensen / MSCA	The important study is the teratogen study in rabbits. The observed effects on fetuses include anomalies and delayed development, but simultaneously also reduced growth and mortality in mothers (3 of 14). The last point obviously seriously toxicity in mothers. Overall, the question is whether there is sufficient evidence for Repr. cat. 2 (suspect) or not being classified for developmental toxicity because the effects caused serious toxicity in mothers. A classification for Repr. cat 2 should be discussed on the following considerations: - Fetuses with the seen effects do not come from the mothers of servere toxicity (death), because they died before delivery. - The positive control showed similar effects on the fetuses WITHOUT mortality of mothers, ie. same effects in fetuses can be seen, although there is maternal toxicity. If the substances have the same mechanism in terms of effects on fetuses, this indicates that the effects on fetuses is not due to the toxicity on the mother - but the mechanism is not known not for either substances. - The CLP criteria says: "Developmental effects which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case-by-case basis that the developmental effects are secondary to maternal toxicity. Moreover, classification shall be considered where	The mechanism of the test substance and the positive control may differ. Comparison of the effects observed with the positive control is therefore useless. The fact that mortality was observed at 45 mg/kg bw indicates severe toxicity occurs at that dose. The dams that survived may also be affected, as indicated by a decreased body weight (clinical signs in dams were not reported). Affected fetuses may come from mothers with severe decreases in body weight (for a precise analysis, individual data are needed). In addition, in the preliminary study mortality was also observed at a slightly lower dose level (30 mg/kg bw/d), indicating that severe toxicity in the dams is present already at a lower dose than 45 mg/kg bw. According to 3.7.2.4.4 of	Noted.

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		there is a significant toxic effect in the offspring, e.g. irreversible effects such as structural malformations, embryo/foetal lethality, significant post-natal functional deficiencies." And in this case it is not proven that the effects are secondary to maternal toxicity and the effects are irreversible. *ECHA comment: The text of the attachment document "Comments for the CLH proposal reg etridiazol.doc" is identical with the text in this table (above).*	Regulation 1272/2008, 'maternal mortality greater than 10% is considered excessive and the data for that dose level shall not normally be considered for further evaluation'. Since 3 out of 14 animals died (21%), the data form the highest dose level should not be evaluated. Since at 15 mg/kg bw no developmental effects were observed, classification is not proposed.	
13/04/ 2012	France / MSCA	p49 Teratogenicity study in rabbit 0, 1.7, 5, 15 and 45 mg/kg bw/day (min 15 pregnant females/group). The results are summarized in table 6.6.2.2 p 49 in the report. Maternal NOAEL 15 mg/kg bw/day based on mortality (3 dams) and stat. sign. decreased body weight at day 18 of gestation. Developmental NOAEL 15 mg/kg bw/day based on a decreased foetal weight (79% of control), a reduction of live foetuses per dam, increase of dams with resorptions. Missing sternebrae (3 foetuses in 3 different litters), tail defects (5 foetuses in 2 different litters), underdeveloped hind limbs (4 foetuses in one litter), crossed hind limbs (7 foetuses in 2 different litters) and open eyes (6 foetuses in 2 different litters) were observed at 45 mg/kg bw. Since no historical control was included, it cannot be excluded that these increases are a consequence of treatment with the test substance. Moreover, the NOAEL for teratogenic effects was set at 15 mg/kg bw/d based on irreversible structural effects. Consequently, these malformations/variations observed the rabbit development study and the limits of the study (no historical control) could justify the classification of etridiazole as Repr 2 H361d. So, FR proposes a classification of etridiazole as toxic for reproduction development category 2 H361 (Repr 2 H361d).	In our opinion it is clear that exposure to etridiazole resulted in the observed developmental effects at 45 mg/kg bw/day. The question is however, whether these effects are a secondary non-specific consequence of the maternal toxicity or not. The CLP criteria state that maternal toxicity above 10% is considered excessive. Since excessive mortality occurred at 45 mg/kg bw/day, the results at 15 mg/kg bw/day (and not 45 mg/kg bw/day) should be used to determine whether classification is necessary. At 15 mg/kg bw, no develeopmental effects are observed and therefore, classification is not proposed.	Also considered.

Respiratory sensitisation- no comments received

Other hazards and endpoints

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC response to comment
12/04/ 2012	Belgium/ MSCA	Environment : * To have a complete view on the degree of bioavailability of the substance it would have been desirable to also have info in the CLH report on adsorption/desorption and volatility * 5.3.1.2 Measured bioaccumulation data Log Kow>3, was the BCF corrected for lipid content? * 5.4.3. Algae and aquatic plants p. 60 The current entry of Etridiazole is based on the latest discussions during a TC C&L in 1997 and added in annex I via the 25th ATP to directive 67/548/EEC (98/98/EC of 15 dec. 1998). The DAR and subsequent updates however date from resp. 2007, 2009 and 2010. As it is not clear on which basis the current classification is decided and which studies are newly introduced, we have nevertheless following question concerning the aquatic toxicity study with Selenastrum capricornutum : Why was the 120h ErC50 taken in account for classification and not the 72h ErC50, while - the classification criterion for aquatic acute toxicity for algae and aquatic plants is an 72h or 96h ErC50 - it can't be assumed that the algae are in the exponential growth phase during the whole exposure period when test duration is longer than 96h - for chronic toxicity the 72h NOEC was used Test duration of an acute toxicity study with algae following OECD201/EEC C.3 is 72h. The test period should only be extended when species grow slower (less than a 16-fold growth in control) than those listed in Annex 2. Was this the case in this study? Pseudokirchneriella subcapitata, (formerly known as Selenastrum capricornutum) is included in annex 2 and considered as a species with a valid growth rate.	Etridiazole has a Henry's law constant of 3.02 Pa m3 mol-1 at 25 °C. In a study (Dzialo, 1994) on the absorption/desorption of etridiazole, the KOC (L/kg) values for etridiazole were 349 (sandy loam, 2.4% oc), 195 (clay, 4.2% oc) and 323 (silt loam, 1.6% oc). Freundlich adsorption isotherm 1/n values were between 0.84 and 0.92. This information should be added to the CLH report. The BCF value has not been corrected for lipid content as the lipid content was not measured in the study. The S. capricornutum study has been revaluated. The coeffecient of variation of the section by section specific growth rate of the control and solvent control appears to be > 35%. This is mainly due to a reduced growth rate observed at 72h and 120 h. Therefore the EC_{50} and EC_{10} of the growth rate, based on linear regression, were calculated for the period between 0-48 h,	Noted.

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			resulting in a value of 0.80 and 0.33 mg/l (based on measured concentrations). These values are comparable to those calculated over the period between 0 -72 h (i.e. 0.80 and 0.22 mg/l, respectively). The acute toxicity classification is now based on the 48-h EC50 in S. capricornutum as this value was considered most in line with the current OECD guidelines. The chronic classification is now based on the 120-h NOEC in *Anabaena flos-aquae.* Despite these changes, the classification proposed for etridiazole remains unchanged.	
12/04/ 2012	Germany / MSCA	Acute toxicity: We agree with the proposed removal of the classifications Acute Tox. 3 *: H331 and Acute Tox. 4 *: H312 as well as of (*) from Acute Tox. 4 *: H302. STOT SE The classification of etridiazole as a respiratory irritant as proposed by the Netherlands (R37, STOT SE 3, H335) is based on clinical evidence obtained in an acute inhalation study (Hilaski, 1994). As usual for studies of this type, histological examination of the upper respiratory tract was not performed in this study. In a subacute inhalative study (Hoffman, 2002), histological lesions were observed that also suggest an irritating potential. The only clinical sign was nasal discharge that may or may not result from irritation. Macroscopic findings were not reported to have occurred, neither in the acute nor in the subacute study. We do not think that there is a sufficient reasoning for classification of	Thank you for the support Since no human data are available with regard to respiratory tract irritation, the available animal studies are used. We agree that in the acute inhalation study, relatively high doses are used (1200 and 5700) mg/m^3). However, in the subacute study, lower doses were used (15-200 mg/m^3) and also in this study effects were observed indicative of	Noted.

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC response to comment
		Etridiazole as respiratory tract irritant (STOT SE 3) as proposed by The Netherlands. The criteria for respiratory tract irritation (STOT SE 3) should be primarily based on human data; for Etriidazole no human data are available. The CLP regulation allows for using relevant animal studies as part of weight of evidence evaluation. Therefore it is our opinion that in case of missing human data the evidence based on experimental animal data should be clear-cut; in the sense that the clinical evidence in acute inhalation studies clearly indicates a specific respiratory tract irritation potential. Etridiazole has been tested with rather high dust concentrations (about 1000 and 5000 mg/m³). It is our general experience that animals try to prevent inhalation of these high dust concentrations; thus we are not astonished that clinical observation of the exposed animals reveal laboured breathing and / or rapid respiration. We assume that this type of clinical symptoms might be frequently observed following these high dust concentrations; thus we prefer to consider these observed effects as a rather general reaction to high concentrations of particles rather than a chemical-specific primary respiratory irritation potential. We recognise that there are no corresponding clear-cut criteria available for STOT SE 3 (respiratory tract irritation). Maybe (in future, not now) we should consider the possibility to have a closer look at the respiratory tract related results of acute dust inhalation studies in order to sort out specific criteria that allow for a differentiation of those substances with a chemical-specific primary irritation potential compared to those which show clinical responses due to substance-independent physical reactions to high concentrations of particles / dust by itself. Skin Sensitisation: We agree with the proposed classification of Etridiazole as Skin Sens. Cat. 1B: H317.	irritation (nasal discharge and squamous metaplasia of the epithelium of the larynx). Metaplasia is an adaptive reaction to local irritation. It is therefore likely that local irritation was induced by inhalatory exposure to etridiazole.We therefore think that there is enough evidence to classify etridiazole as R37, STOT SE 3, H335 Thank you for the support	
13/04/ 2012	Spain / MSCA	p 21. Conclusions on classification and labelling of acute oral toxicity Etridiazole is currently listed in Annex VI of 1272/2008/EEC Regulation	Thank you for the support	Noted.

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC response to comment
		(CLP) – included in 25th ATP of Directive 67/548/EEC (DSD). The current classification for acute oral toxicity is as follows: Acute Tox. 3 H331 (minimum classification), Acute Tox. 4 H312 (minimum classification) and Acute Tox. 4 H302 (minimum classification) under the CLP Regulation and T; R 23 and Xn; R 21/22 under the DSD. The Spanish CA supports the proposed classification of etridiazole as Xn, R22: Harmful if swallowed (limits 200< LD50 ≤ 2000 mg/kg bw) and as Acute Tox 4 (H302: Harmful if swallowed) (limits 300< LD50 ≤ 2000 mg/kg bw) according to DSD and CLP classification criteria, respectively. This classification is based on the LD50 value in male (LD50 = 1141 mg/kg bw) and female (LD50 = 945 mg/kg bw) obtained in the oral toxicity study in rats (Warshawsky LD, 1994). Considering the results obtained in the dermal toxicity study (LD50 > 5000 mg/kg bw; Warshawsky LD, 1994) and in the acute inhalation toxicity study (CL50 > 5.7 mg/l/4 h; Hilaski RJ, 1994) the existing classification seems inappropriate and etridiazole should not be classified for acute dermal and inhalation toxicity, according to both CLP and DSD classification systems. However, the basis for the current classification is unknown. Therefore, before removing the classification for dermal and inhalation toxicity it should be useful to verify on which data were based, in order to have into account all available data. p 22. Respiratory tract irritation The Spanish CA supports the proposal of the dossier submitter, to classify etridiazole as Xi; R37: Irritating to respiratory system under DSD criteria. Similarly, according to CLP criteria, etridiazole can be classified for specific target organ toxicity after single exposure as STOT SE 3, H335; May cause respiratory irritation. Findings observed in acute inhalation study (Hilaski RJ, 1994) and subacute inhalation study (Hoffman, 2002) in rats are considered signs of reversible respiratory tract irritation: laboured breathing, rapid respiration immediately after exposure and the histopathological data from the respiratory system (squamous metaplasia in the seromucinous glands of the larynx). p 24. Conclusions on classification and labelling of skin sensitisation The Spanish CA supports the proposed classification of etridiazole as Xi; R43 May cause sensitization by skin contact according to DSD (when an adjuvant type guinea pig test method for skin sensitisation is used, a	Thank you for the support Thank you for the support	

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC response to comment
		response of at least 30 % of the animals is considered as positive) and as Skin Sens 1B, H317: May cause an allergic skin reaction according to the 2nd ATP of CLP Regulation (in a guinea pig maximisation test with >1% intradermal induction dose a response ≥ 30% of the animals is considered as positive). This classification is based on the results of the dermal maximisation study in guinea pigs (Parcell BI, 1993) where positive response was obtained in all test animals (100%) using 20% of test article for intradermal induction dose. p 27. Specific target organ toxicity (CLP Regulation) - repeated exposure (STOT RE) The dossier submitter is of the opinion that etridiazole does not need to be classified for specific target organ toxicity. Besides, etridiazole is currently included in Annex VI of the CLP regulation and it is not classify with respect to Specific Target Organ Toxicity. Nevertheless, the Spanish CA would like to highlight, for the RAC´s consideration, some findings observed, on the basis of which a classification could be established. In the 90 days in rats study (Richards, 1994) some alterations were observed which may represent a hypercoagulable state typical of chronic disorders: at the end of the exposure period platelet count was increased in males at 64.7 mg/kg bw/d and females at 73.6 mg/kg bw/d, prothrombin time and activated thromboplastin time (APTT) were significantly decreased in males from 29.5 mg/kg bw/d, APTT was still decreased at 29.5 mg/kg bw/d at the end of the 4-week recovery period. This is supported by the alteration observed in the 18 month study in mouse (Goldenthal, 2004) where thrombus formation was observed in the heart at higher doses (184.7 and 221.7 mg/kg bw/d in males and females, respectively). The CLP regulation explicitly covers significant/severe reversible effects for target organ toxicity after repeated exposure. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed are included. STOT-RE is assigned on the basis of findings of "significant" or "severe" toxicity. In this context 'Significant' means changes which clearly indicate functional disturbance or morphological changes which are toxicologically relevant. 'Severe' effects	Thank you for raising this issue. We agree that these effects were observed at relevant dose levels and could be considered for STOT RE. However, the effects on PTT and APTT are only minor: < 20% and only observed in males and not in females. Further, no increased thrombus formation was observed at these dose levels in the 13-week study. Thrombus information should be considered as clear evidence of functional impairment of the clothing system. The absence of such effects could be seen as an indication that the effects are minor and not warrant classification with STOT RE. The effects on platelet count are small (126%), only significant in females and, on their own, do not indicate significant toxicity. The increase in reticulocytes is also only small (146%), significant in females only and on their own, do not indicate significant toxicity. Increases in reticulocytes are normally associated with increased breakdown of RBC. This is not observed in this study. Combination of the decreases in clothing time and the	The comments were considered in the draft opinion.

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC response to comment
		are generally more profound or serious and indicates changes that are of a considerably adverse nature with a significant impact on health (CLP regulation). On the other hand, classification with R48 (DSD) is reserved only for substances that cause serious damage to health. The alterations mentioned above occurred after repeated exposure below the DSD and CLP classification criteria (< 50 mg/kg p.c /day and < 100 mg/kg p.c /day). It is doubtful if these alterations could be regarded as serious. However, they might be considered significant effects. Consequently, there is a need to look into this issue in depth, as the overall weight of evidence could appear sufficient for a classification at least as STOT RE Cat. 2, H373: May cause damage to organs through prolonged or repeated exposure according to the CLP Regulation.	increase in reticulocytes is not correct as the effects on clothing are observed in males but the effects on platelets and reticulocytes in females. Therefore, we think it is not necessary to classify etridiazole for STOT-RE.	
13/04/ 2012	France / MSCA	Page 53 : Paragraph related to degradation in water system: It should be interesting to precise that the values reported for two water/sediment systems (Schanné C., 1998), 1.78d, 1.92d (...) are minimum half-lives values. Pages 53-54 : Paragraph related to degradation in soil : The tables 14a and 14b reported in the page 54 are those from the DAR while they are not in the final list of endpoints from the EFSA journal related to the peer review of the pesticide risk assessment of the active substance etridiazole. Then these tables should be withdrawn. Indeed, according to the EFSA journal 2010 of etridiazole, no reliable information is considered available for etridiazole and dichloro-etridiazole. As a consequence the quantitative information reported on page 53-54 of the CLH report should be revised. However, the non-reliable information that is available indicates that the persistence of etridiazole might be classified as low to medium. Therefore no change in the final conclusion is expected. Regarding environmental hazards, we agree on the proposed classification for etridiazole.	The two reported values are the DT50 system values for the two systems tested. The studies of Nag & Yu (1994), Nag & Regis (1998) and Völkel (2000) are considered valid in the DAR (see e.g. DAR addendum May 2010) although these studies have some limitations. We therefore consider the results valid and prefer not to withdraw them for the reason of unacceptability. However, the results of the soil studies are not used for classification and labelling since sufficient valid data for the aquatic environment is available. The added value of soil degradation data in the classification decision when adequate aquatic degradation studies are	Noted.

Date	Country / Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC response to comment
			available is unclear and should be discussed in the RAC for additional guidance. Thank you for the support of the classification proposal	

ATTACHMENTS RECEIVED: 1

1. **Comments for the CLH proposal reg etridiazol.doc** submitted by Denmark, MSCA. Attachment is identical with the text in the table.