Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

hymexazol (ISO); 3-hydroxy-5-methylisoxazole

EC Number: 233-000-6
CAS Number: 10004-44-1

CLH-O-0000001412-86-229/F

Adopted

14 September 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON HYMEXAZOL (ISO); 3-HYDROXY-5-METHYLISOXAZOLE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: hymexazol (ISO); 3-hydroxy-5-methylisoxazole
EC number: 233-000-6
CAS number: 10004-44-1
Dossier submitter: Finland

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	France		MemberState	1
Comment received				
No comment on physical hazards: hymexazol is not classified based on physical or chemical properties.				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Sweden		MemberState	2
Comment received				
Overall, the reliability of the studies (according to ECHA´s Klimisch scores 1-4) are missing.				
Dossier Submitter's Response				
Thank you for your comment. DS did not use the Klimisch score system and it is not possible to modify the CLH report anymore. However the reliability of each of the studies is expressed as a key study or as a supportive study.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
28.11.2017	Germany		MemberState	3
Comment received				
From our point of view, it makes sense when harmonizing the classification as Acute Tox 4				

also to harmonize the corresponding ATE value. This enables a consistent classification of hymexazole mixtures.
Dossier Submitter's Response
DS agrees with the comment however the ATE values were not proposed in the CLH dossier and therefore this will remain as a task for RAC.
RAC's response
Thanks for the comment. Regarding the converted ATE value, the Cat 4 will be converted to 500. However, all preparations will be tested for acute toxicity according to the pesticide directive.

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Belgium		MemberState	4
Comment received				
As a general comment, we regret the absence of evaluation of STOT RE endpoint while the repeated-toxicity studies might have been sufficient to warrant a STOT RE classification.				
Dossier Submitter's Response				
Thank you for your comments. The data on repeated dose toxicity was included in the CLH report only to provide an overview of the general toxicity of the substance, we did not evaluate repeated dose toxicity in the CLH dossier.				
RAC's response				
Thanks for the comments. STOT RE has not been assessed in the dossier. A summary is included in the ODD for all 28 and 90 days studies. It seems like liver and thyroid weight changes are predomminatly among the studies and changes in blood chemisty. The LOAEL values are however relative high (>300 mg/kg bw/d for 28 days studies, >100 mg/kg/d for 90 days studies and > 25 mg/kg bw/d for 1 year). Nethertheless, as the endpoint is not evaluated by the DS, RAC don't have the possibility to propose a classification.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
28.11.2017	Germany		MemberState	5
Comment received				
Based on the developmental toxic effects observed in rabbits (incomplete inferior vena cava) and rats (foetal body weight, skeletal variations) the proposal by the DS to classify Hymexazol as Repr. 2, H361d (Suspected of damaging the unborn child) is supported: The findings in rabbits were not considered secondary to maternal toxicity and effects in rats were clearly observed in the absence of maternal toxicity. However, the incidence of incomplete inferior vena cava was only observed in rabbits with low incidence and in some cases associated with maternal toxicity at higher dose, therefore Repr. 1B is considered not appropriate. With regard to fertility, the DS considered 'some adverse effects upon the reproductive parameters were observed however the magnitude of the effects (prolonged gestation, reduced litter size) does not justify classification'. However, based on the comprehensive presentation in the CLH report, clear effects on reproduction and offspring development became apparent in a preliminary (one-generation) study at high doses of 5000 and 10000 ppm with a threshold that might be in the magnitude of 2500 ppm. In the main (two-generation) study at highest dose level litter size was significantly reduced [post implantation survival index 91 % in control animals, 74 % at 2500 ppm] and gestation				

slightly prolonged without clear concomitant evidence of parental toxicity.
Due to the increase of reproduction effects without parental toxicity in both generation studies, an additional classification for Hymexazol as Repr. 2, H361f (Suspected of damaging fertility) is proposed.

Dossier Submitter's Response

Thank you for your comments and support for Repr. Cat 2, H361d classification.

DS agrees that some of the observations made might be considered as adverse effects on fertility and these should be discussed at RAC. However DS would like to present some additional arguments regarding gestation length and reduced litter size.

Gestation length: In the main two-generation reproductive toxicity study there was a slight tendency towards longer gestation lengths in both F0 and F1 generations. At 2500 ppm the gestation was prolonged by half a day (5 %, 1/21 of the F0 and F1 dams delivered on day 24) which was statistically significant only in the F1 generation. In the preliminary range-finding reproductive toxicity study at 2500 ppm 2 dams delivered on day 22.5 and 4 dams delivered on day 23, and at a higher 5000 ppm dose one dam delivered on day 25, the other dams delivered on day 23 (2 dams) and on day 23.5 (2 dams).
In the tables below laboratory background control data on gestation lengths for F0 (20 studies) and F1 (22 studies) females are shown (not included in the CLH dossier).

F0 females					
Gestation (days)	22	22.5	23	23.5	24
Mean (%)	10	33	46	9	1
Low (%)	0	19	20	0	0
High (%)	35	50	67	20	15

F1 females					
Gestation (days)	22	22.5	23	23.5	24
Mean (%)	10	33	44	10	1
Low (%)	0	18	16	0	0
High (%)	35	50	67	32	15

Based on the background data the length of gestation in the treated dams in the main study at 2500 ppm is above the mean but within the range of the historical control values. In the preliminary study at 5000 ppm the gestation length for 1 dam (parturition on day 25) is outside the background data values.
Despite the slight prolongation of gestation the outcome of the pregnancies was not affected for any dam. There were no difficulties in parturition and the birth weights of the F1 and F2 pups were not different from controls in the main study. In the preliminary study the at 5000 ppm the pup weights at birth were lower than in control.
In the main study the gestation index (percent of of live litters born per pregnant females) was reduced to 91% at 2500 ppm for F0 females due to one dam dying before parturition and one dam presumably having cannibalized her offspring. For F1 females the gestation index was 100%.
Taken together, DS is of the opinion that the biological significance of a slightly prolonged gestation is of low concern because other fertility parameters were not affected.

RAC's response
RAC agrees with the DS.

Date	Country	Organisation	Type of Organisation	Comment number
30.11.2017	United Kingdom	Mitsui Chemicals Agro, Inc.	Company-Manufacturer	6

Comment received

The manufacturer submitted to the Dossier Submitter (Finland – Tukes) the report of a new investigation designed to demonstrate the effect of hymexazol on the formation of the inferior vena cava of the rabbit fetus. In this investigation, the health conditions of maternal rabbits were checked in detail more than required by the regular testing guideline.

In this new investigation, a developmental abnormality of inferior vena cava was not reproduced at the dose level of 350 mg/kg bw/day even though some depletion of health conditions were detected on the maternal rabbit of this group. On the other hand, the severe depletion of maternal health that lead to humane early termination were observed at 450 mg/kg bw/day and above. Comparable clinical symptoms that lead to early termination had been also observed among the original rabbit prenatal developmental toxicity (PNDT) study and its dose range finding studies at the same dose groups with new investigation (equal to 450 mg/kg and above).

Since incomplete formation of inferior vena cava did not occur at 350 mg/kg bw/day in the new investigation, it strongly suggests that the occurrence of incomplete vena cava on one of 110 fetus at 150mg/kg bw/day in the original PNDT study was a spontaneous non-treatment related event. In addition to that, it is expected that the maternal rabbits of 450 mg/kg bw/day groups in the original developmental study had suffered adverse health that could not be revealed without clinical pathological examinations. This suggests that the occurrence of incomplete vena cava of three of 108 fetus at 450 mg/kg bw/ day was secondary to maternal toxicity of hymexazol.

In either event, a classification of Repr. Cat 2, H361d, Possible risk of harm to the unborn child, is not warranted because direct embryo-fetal toxicity would not be an inherent property of hymexazol.

Refer to attached position papers (Hymexazol_H361d Comments 20171128_confidential version_sanitised and Hymexazol_Fetal development position paper_confidential_sanitised). Details of the authors of the vertebrate studies and position paper have been redacted.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Hymexazol_Fetal development position paper_confidential_sanitised.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Hymexazol_Fetal development position paper_confidential.zip

Dossier Submitter's Response

Thank you for your comments.
The new studies received are included in the CLH report (see chapter 4.11 Toxicity for reproduction, p. 39-). More specifically studies: a dose range finding toxicity study in the pregnant New Zealand White rabbit by oral gavage administration (IIA 5.6.2/06) and a study of maternal effects and embryo-fetal development effects in the New Zealand White rabbit by oral gavage administration (IIA 5.6.2/07). DS is of the opinion that negative findings in these studies do not overrule the findings in the key rabbit teratology study (IIA,

5.6.2/05). The observed developmental toxic effects in rabbits (incomplete inferior vena cava) were not considered secondary to maternal toxicity. An incomplete inferior vena cava was observed in one foetus at a middle dose of 150 mg/kg bw/day which was not maternally toxic. At a maternally toxic dose of 450 mg/kg bw/day two more foetuses in two different litters had incomplete inferior vena cava. In addition, one dam having less significant maternal toxicity at 450 mg/kg bw/day had a foetus with incomplete inferior vena cava. The incidence of incomplete inferior vena cava (1.83 %) was above the historical control value (range from 0 to 0.46 % over the years 1990-1995) thus questioning the spontaneous nature of the abnormality. Since malformations of inferior vena cava are relevant for humans, classification should be considered.
RAC's response
RAC realised that no treamtment related effects were seen in the two studies from 2015, however, the negative findings in those studies cannot overrule the findings in rabbits in the key study /05. However, this will be discussed in plenar.

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Denmark		MemberState	7
Comment received				
Denmark supports the suggested classification (H361d)				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Belgium		MemberState	8
Comment received				
Fertility: BECA does not agree with the dossier submitter on the proposal to not classify hymexazol for fertility effects. Indeed, in a two-generation reproduction study in rat (key study, II.A, 5.6.1/02), adverse signs on fertility were identified such as: an extension of the gestation length in F0 and F1 females at 2500 ppm, as well as a reduction in litter size due to an increase in post-implantation loss in F0 and F1 females at 2500 ppm. The gestational index was therefore reduced (only in F0). These signs were observed at a dose that did not induce maternal toxicity. Furthermore, the NOAEL for reproductive effects was inferior to the NOAEL for maternal effects (500 ppm v.s. 2500 ppm, respectively), increasing the concern. Moreover, these results are supported by a preliminary reproductive toxicity study in rat (II.A, 5.6.1/01) where a decrease of the gestational index and an increase in the total number of resorptions were seen at 5000 and 10 000 ppm. In addition, a decrease in the number of implantation sites and an increase in the gestational length was observed to appear in a dose-dependent way. BECA would also like to point out that the control group data used for the key study raise questions on their validity. We are concerned by data showing, for example: - Gestational length of 23 or 23.5 days in 16 and 32 % of F0 control females and 32 and 21 % in F1 control females, respectively - A negative body weight gain (-1g) in F1 females				

- Irregular or acyclic estrous cycle affecting 13 and 21% of F1 females, respectively
- A viability index on PND4 of only 81 % in F1 offspring
- 40 pups out of 9 litters dying before terminal kill in F1 pups

Perhaps this should lead to a thorough review of the data since it might a misinterpretation of the dataset.
In brief we consider hymexazol should be classified for fertility effects and we propose : Repr. 2; H361f.

Development:
BECA does not support the proposal to classify hymexazol as Repro. 2; H361d.
Indeed, in a two-generation reproduction study in rat (key study, II.A, 5.6.1/02), a significant decrease in post-implantation survival index and in litter size was observed after dams were exposed to 2500 ppm (dose which did not induce maternal toxicity). These results were reproducible between the F1 and the F2 offspring.
In a key teratogenicity study in rat (IIA, 5.6.2/02), fetal weight was significantly decreased after dams were exposed throughout gestation to 500 mg/kg bw/d of hymexazol. A significant increase in thorax and abdomen anomalies was observed in pups of dams exposed to the highest dose (500 mg/kg bw/d). Subcutaneous haemorrhages were also seen to increase in a dose-dependent way from the middle dose, and it was significant at the highest dose and an increase in the incidence of skeletal findings was observed at 500 mg/kg bw/d.
Moreover, a dose-dependent increase in post implantation loss can also be highlighted although the impact of the substance at the highest dose is probably masked by the preceding increase in pre-implantation loss. Furthermore, the NOAEL for embryotoxicity/teratogenicity (100 mg/kg bw/d) is inferior to maternal NOAEL (500 mg/kg bw/d), increasing the concern on the reprotoxic potential of hymexazol.
In a key teratogenicity study in rabbit (IIA, 5.6.2/05), a dose-dependent increase in post-implantation loss was seen. Exposure to a non-maternotoxic dose of 150 mg/kg bw/d lead to an increase of nearly 25% of post-implantation loss, which is non negligible, compared to the control group.
A slight dose-dependent increase in the incidence of malformation was observed, and incomplete inferior vena cava (a rare and severe malformation) was detected in (0, 0, 7 and 14 % of the litters examined which were exposed to 0, 50, 150 and 450 mg/kg bw/d, respectively). This malformation already appeared at a non-maternotoxic dose.
Furthermore, the embryotoxicity/teratogenicity NOAEL (50 mg/kg bw/d) was inferior to maternal NOAEL (150 mg/kg bw/d), increasing the concern about the potential of hymexazol to induce reprotoxic effects.
Considering exposure to hymexazol lead to a decrease of the fetuses weight, and to an increase in post-implantation loss as well as in severe effects such as subcutaneous hemorrhages in rat or heart and great vessels malformation in rabbit, maybe more attention should be given to the interpretation of the data. As two species are affected, dose-dependency was showed for several effects and it cannot be ruled out that the underlying mechanisms cannot be the same in humans, perhaps a classification as Repr. 1B; H360D.
In conclusion, BECA proposes to classify hymexazol as Repr. 1B, H360fD.

Dossier Submitter's Response

Thank you for your comments.

Fertility
Please see our response to Germany CA regarding prolonged gestation length and reduced litter size (comment no 5).

Regarding the quality of the main two-generation reproductive toxicity study and the control animals:
The study was conducted according to GLP or according to guidelines relating to non-clinical studies. In the study report there were no comments recorded regarding the issues raised by BECA for the control animals.

Gestational length of 23 or 23.5 days in 16 and 32 % of F0 control females and 32 and 21 % in F1 control females, respectively
DS agrees that the gestation length in the control F0 animals is outside the background control values on day 23.5. For the control F1 animals the gestation lengths are within the laboratory background data values. Despite of the pattern of gestation lengths of the control animals, the conclusion regarding the gestation length in the treated groups is not changed.

A negative body weight gain (-1g) in F1 females
DS agrees that there was an atypical body weight change during the lactation period and this was true with all the dams (both control and treated). The reason for the large variation in the mean body weight gain is not known.

Irregular or acyclic estrous cycle affecting 13 and 21% of F1 females, respectively
Since in the treated dams there were no effects on estrous cycle the conclusion of the outcome of the study is not changed.

A viability index on PND4 of only 81 % in F1 offspring
DS agrees that the viability index at PND4 in the F1 offspring was low in the control group. However the same parameter was 100% in the F2 offspring. The reason for F1 pup mortality between day 1 and 4 is not known. The lactation index remained unchainged. However since in the treated groups the viability index on PND4 (96-97%) did not change the conclusion of the outcome of the study is not changed.

40 pups out of 9 litters dying before terminal kill in F1 pups
The original study data does not reveal any reasons why there was high mortality among the F1 pups in the control group. There were 3 dams who lost most of the pups (one dam lost her whole litter). Individual pup data indicates that a common finding was that the dead pups did not have milk in the stomach. Nevertheless, this mortality in the control group might be incidental. Similar mortality in F2 control pups was not seen.

Development:

Pre- and post-implantation loss

In a key teratogenicity study in rat (IIA, 5.6.2/02) dose-dependent increase in post-implantation loss was seen at the low and middle dose group (2.9, 6.4, 8.3 and 1.6 % at dose levels of 0, 20, 100, 500 mg/bw/day, respectively). Effect on post-implantation survival was not evident at the highest dose, but at the highest dose, there was preceding slight increase in preimplantation loss (6.0, 9.1, 6.0 and 10 % at dose levels of 0, 20, 100, 500 mg/bw/day, respectively). There was also increase in pre-implantation loss at the lowest dose but no similar impact on post-implantation loss was seen. The dosing started on day 6 p.c., probably after the time of implantation. The foetal weight was reduced statistically significantly (10 %) at the highest dose level group (500 mg/kg bw/day) when compared to concurrent control. At the highest dose no maternal toxicity was observed. Effects on implantation were not statistically significant from concurrent control. Incidences of post-implantation loss at the low and middle dose group were above the mean value of laboratory background controls but were within the range of those control values (not

included in the CLH report) from 36 studies on this rat strain (pre-implantation loss: mean 9.0, range 4.9-27.2 %; post-implantation loss: mean 5.52, range 1.90-10.90 %). DS agrees that there are some indications of increase in post-implantation loss at the low and middle dose groups but does not consider this evidence sufficiently convincing to change the proposed classification.

In a key rabbit teratogenicity study in rabbit (IIA, 5.6.2/05) a dose dependent increase of post-implantation loss was seen of 8.3 %, 23 % and 70 % at dose levels of 50, 150 and at 450 mg/kg bw/day compared to control group (10.8, 11.7, 13.3, 18.4 % at dose levels of 0, 50, 150 and at 450 mg/kg bw/day groups, respectively). Higher post-implantation loss at the highest dose level was a consequence of slight increase in late embryonic deaths. The litter size was slightly reduced (12.5 %). There was a preceding increase of pre-implantation loss of 52 % and 20 % at the middle and high dose groups (16.4, 15.1, 25.0, 19.6 % at dose levels of 0, 50, 150 and 450 mg/bw/day groups, respectively). Numbers of corpora lutea were slightly higher at the middle dose than controls, which may account in part for the slightly increased pre-implantation loss (number of implants was similar in all groups). The dosing started on day 7 p.c., probably after the time of implantation. The highest dose level (450 mg/kg/bw/day) was maternally toxic but the middle dose level (150 mg/kg bw/day) was not. Therefore, it is not possible to conclude that effect on post-implantation loss was secondary to maternal toxicity. However, the differences in late embryonic deaths and pre- and post-implantations losses were not statistically significant when compared to concurrent controls. The incidences of post-implantation loss at the middle and high dose dose level were above the mean value of historical controls. At the middle dose level it was within the range of historical control data and at the highest dose level it was slightly above the range values from historical control data (Froxfield historical control data: pre-implantation loss: mean 17.5, range 13.2-22.7 %; post-implantation loss: mean 12.6, range 9.5 to 16.2 %, seven studies, over the years 1990-1992). DS agrees that there were some indications of increase in post-implantation loss at the middle and high dose groups but does not consider this evidence sufficiently convincing to change the proposed classification.

In conclusion, there were some indications of increase in post-implantation loss in the studies described above and in addition in the rat two-generation reproductive toxicity study and in the preliminary reproductive toxicity study in rat. DS does not consider this evidence sufficiently convincing to change the proposed classification from Repr. Cat 2 to 1B, however this should be discussed at RAC.

Subcutaneous hemorrhages

In a key teratogenicity study in rat (IIA, 5.6.2/02) in addition to reduced foetal weight and increased incidence of foetuses with skeletal variations, there was an increase in thorax/abdomen anomalies and subcutaneous hemorrhages at the highest dose group in the absence of maternal toxicity (namely nasal, cranial, jaw, submandibular, abdominal and limbs). Some of the incidences of subcutaneous hemorrhages were increased in a dose-dependent way but not all when compared with concurrent control and lower dosage groups (see table 1 below). These findings were not statistically different from concurrent control. All incidences were above the mean values of laboratory background control data of this rat strain but most of the values were within the background control ranges (not included in the CLH report). However, when taking into account the malformations on heart and/or great vessels (i.e incomplete inferior vena cava) seen in the key rabbit teratogenicity study (IIA, 5.6.2/05), DS agrees that the subcutaneous hemorrhages seen in the absence of maternal toxicity are additional concerns for classification of developmental toxicity. Overall,

however, DS considers that the severity and magnitude of incidence of observed effects does not warrant to change the proposed classification from Repr. Cat 2 to 1B.

Table 1.Foetal findings

Parameter	Control	20 mg/kg bw/day	100 mg/kg bw/day	500 mg/kg bw/day	Laboratory background control data[b]	
					Mean	study ranges
Selected internal findings in foetuses (free-hand serial)[a] No. of foetuses/litters examined	179 / 24	169 / 24	164 /23	156 /21		
Thorax and abdomen						
Space between organs and body	0	0	0	**2.6 (3)**	2.32	0.0-8.9
Small conal septal defect	0	0	0	**0.6 (1)**		-
Abdominal haemorrhage	1.1 (2)	1.2 (2)	0.6 (1)	**3.2 (5)**	2.22	0.0-5.5
Unilateral hydronephrosis	0	0	0.6 (1)	**3.8 (4)**	1.12	0.0-4.2
Bilateral hydronephrosis	0	0	0	**1.9 (2)**	0.6	0.0-7.3
Unilateral hydroureter	5.6 (7)	3.0 (4)	4.3 (4)	3.8 (4)	9.17	2.8-19.5
Bilateral hydroureter	3.4 (4)	1.8 (3)	1.8 (3)	**7.7 (8)**	4.88	0.0-21.9
Subcutaneous haemorrhage(s)						
Nasal	0	0	0.6 (1)	**1.9 (3)**	1.04	0.0 - 4.3
Cranial	1.1 (2)	1.2 (2)	2.4 (4)	**4.5 (5)**	3.26	0.0 - 14.1
Jaw	3.9 (3)	5.3 (5)	6.1 (6)	**8.3 (7)**	4.88	0.0-15.4
Submandibular	1.1 (2)	0.6 (1)	1.2 (2)	**10.3 (8)**	2.04	0.0-7.1
Fore-/hind-limb(s)	11.7 (9)	7.7 (9)	11.6 (11)	**21.2 (12)**	19.11	0.0-38.3
Abdominal	0	1.8 (2)	1.2 (2)	**3.8 (5)**	1.35	0.0-8.3

[a]Incidence (%) (No. of litters)
[b]30 studies (4013 foetuses)

RAC's response

Fertility:
RAC agrees with the DS and consider that the biological significance of a slightly prolonged gestation is of low convern, as other fertility parameters were not affected.

Developmental effects:
RAC has identified three crucial effects that are relevant for classification of the substance as toxic to the development. One of the effects is the incidences of incomplete inferior vena cave and the other is the incidences of anomalies together with subcutaneous hemorrhages and the last is post/pre implantation loss. However, RAC agrees with the DS assessment for both post-implantations loss and the incidences of anormalites observed. However, this indeed need to be discussed in RAC plenary.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Denmark		MemberState	9
Comment received				
Denmark supports the suggested classification (Acute Tox. 4; H302)				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Belgium		MemberState	10
Comment received				
BE CA agrees with the re-classification as acute tox 4 (H302). The two OECD 401 TG studies for oral toxicity of hymexazol present similar LD50 in rat and mouse (1600 mg/kg bw/day in males). Therefore criteria's for an Acute Tox 4 (oral) classification are met.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Denmark		MemberState	11
Comment received				
Denmark supports the suggested classification (Eye Dam. 1; H318)				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted – the classification is, however, part of the current classification and will not be discussed by RAC.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Sweden		MemberState	12
Comment received				
Based on the information available in the CLH report, the Swedish CA agree with the proposed classification Skin Sens 1B, H317				
Dossier Submitter's Response				
Thank you for your comment. However please see our response to comment no 15.				
RAC's response				
RAC agrees that subcategorization is not justified in this case, and propose Skin Sens. 1; H317.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON HYMEXAZOL (ISO); 3-HYDROXY-5-METHYLISOXAZOLE

Date	Country	Organisation	Type of Organisation	Comment number
28.11.2017	Germany		MemberState	13
Comment received				
We propose to classify hymexazol as Skin Sens. 1 (CLH dossier: Skin Sens. 1B). Justification: In the Key study IIA, 5.2.6/02, GPMT was performed using only one concentration. Accordingly, a potency that is mandatory for sub-categorisation in 1A or 1B by the use of animal test data, could not be deduced from this assay submitted.				
Dossier Submitter's Response				
Thank you for your comment. Please see response to comment number 15.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Denmark		MemberState	14
Comment received				
Denmark supports the suggested classification (Skin Sens. 1B; H317)				
Dossier Submitter's Response				
Thank you for your comment. However please see our response to comment no 15.				
RAC's response				
Noted, however, subcategorization is not justified in this case, and therefore RAC propose Skin Sens. 1; H317.				

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Belgium		MemberState	15
Comment received				
The only admissible study regarding skin sensitization in the dossier is the OECD 406 Maximisation Guinea Pig study (IIA, 5.2.6/02). The results showed 50% positive skin reactions in hymexazol treated animals (1,5% w/v first intradermal induction) at 24h and 48h after the challenge. These findings are consistent with a Skin sens 1B categorization (≥ 30% responding at > 1% intradermal induction dose), provided that Category 1A is excluded. No information is available on skin sensitization at doses warranting a Skin sens 1A classification. The Buehler test being disregarded because of too low animal number and concentration (no mild irritation), there is also no other available information to support a Skin Sens 1B or no classification. Therefore a Skin sens 1 classification, without subcategorization, should be considered for hymexazol.				
Dossier Submitter's Response				
Thank you for your comment. DS agrees that the available data is not sufficient to exclude subcategory 1A. Hymexazol has not been tested at doses which could warrant classification as Skin sens. 1A. Therefore, subcategorization is not possible and classification should be Skin sens. 1; H317.				
RAC's response				
RAC agrees that subcategorization is not justified in this case, and propose Skin Sens. 1; H317.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
28.11.2017	Germany		MemberState	16
Comment received				
page 6ff: Proposed harmonised classification and labelling (Table 3): We support the proposal of classification for environmental hazards as Aquatic chronic 2 (H411).				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	France		MemberState	17
Comment received				
We agree with the classification proposal.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Sweden		MemberState	18
Comment received				
The Swedish CA agrees with the proposal to classify hymexasol as Aquatic Chronic Category 2 (H411). Under section 5.4 : the text in table 74:summary of relevant information on aquatic toxicity, should be moved to the next page together with the table. Also the "=" is missing on some of the EC50, EC10 and NOEC factors in the presentation of the results in the same table.				
Dossier Submitter's Response				
Thank you for your comment. We apologise these editorial mistakes. Unfortunately, according to current RAC procedure, the CLH-report cannot be changed at this stage of the process.				
RAC's response				
Thank you for your comment. RAC is of the opinion that the editorial mistakes do not affect the overall assessment of the substance.				

Date	Country	Organisation	Type of Organisation	Comment number
30.11.2017	United Kingdom	Mitsui Chemicals Agro, Inc.	Company-Manufacturer	19
Comment received				
In the 'Chronic aquatic toxicity' section of Section 5.5 'Comparison with criteria for				

environmental hazards (section 5.1-5.4)' of the CLH Report for Hymexazol the following text is currently proposed:
"No adequate chronic data is available for all three trophic levels, thus the classification of hymexazol to the chronic category is assessed using two approaches according to CLP (2nd ATP):
1. In the case of non-rapidly degradable substances, for which there are adequate chronic toxicity data available, H411 classification is applicable based on EC10 value of 0.4 mg/l (≤ 1 mg/l).
2. When adequate chronic toxicity data are not available classification is based on the combination of acute aquatic toxicity data and environmental fate data. Hymexazol is non-rapidly degradable and has a low potential for bioaccumulation. Therefore,
no chronic aquatic classification is applicable based on 96 h LC50 value (for fish) of >100 mg/l and the log Kow < 4. "
The most stringent outcome shall be chosen and therefore hymexazol shall be classified as Aquatic Chronic Category 2, H411 according to Regulation EC 1272/2008."
The applicant respectfully notes that the 2nd environmental classification approach should consider all the available acute data for hymexazol not just the acute data available for fish. The lowest acute endpoint for hymexazol is the Lemna gibba IC50 value of 9.4 mg/L would lead to the Aquatic Chronic Category 2 classification.
This would mean that classification based on all the available chronic data for hymexazol and separately all the available acute data for hymexazol both lead to the Aquatic Chronic Category 2, H411 classification according to Regulation EC 1272/2008.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Hymexazol_Fetal development position paper_confidential_sanitised.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Hymexazol_Fetal development position paper_confidential.zip

Dossier Submitter's Response

Thank you for your comment. When adequate chronic data does not exist for all three trophic levels surrogate method is used. As explained in EHCA guidance (Guidance on the Application of the CLP Criteria) when using surrogate approach, and comparing acute data with environmental fate data, the lowest acute test result from tropic levels for which there is no chronic data available are considered. For hymexazol, there is chronic data available for Daphnia, algae and Lemna but not for fish. Therefore, in this specific case, in the surrogate approach the acute test result is only used for fish (LC50 > 100 mg/l), not for the other trophic levels, and this would result no chronic aquatic classification for hymexazol. However, the most stringent outcome will be chosen.

RAC's response

Thank you for your comment. RAC agrees with the DS that the surrogate chronic data apply only to fish. In the case of hymexazol, adequate chronic toxicity data are available for algae, aquatic plants and aquatic invertebrates but not for fish. According to the CLP Regulation (Section 4.1.2.3), 'in the absence of adequate chronic toxicity data, the subsequent step is to combine two types of information, i.e. acute toxicity data and environmental fate data (degradability and bioaccumulation data).' The surrogate chronic data is used where no chronic data are available for a particular trophic level. Using Figure 4.1.1 of the CLP Regulation as guidance we have the following classifications:

- Based on chronic data for the most sensitive trophic level, i.e. aquatic invertebrates: EC_{10} is 0.4 mg/L and non-rapidly degradable which leads to classification Aquatic Chronic 2
- Based on surrogate chronic data for fish: LC50 of > 100 mg/L and non-rapidly degradable which leads to no classification.

The most stringent outcome must be used for classification, Aquatic Chronic 2 based on the

chronic data.

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Denmark		MemberState	20
Comment received				
Denmark agrees with the classification				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted				

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2017	Belgium		MemberState	21
Comment received				
Aquatic Acute toxicity BE CA agrees that classification for Aquatic acute toxicity is not warranted (14dEC50 Aquatic plant L. giba =9.4 mg/l). However the general exposure period according to OECD221 and US EPA 850.4400 is 7d. Aquatic Chronic toxicity : Based on the most stringent outcome for the chronic aquatic toxicity (NOEC/ECx and surrogate approach) it is warranted to classify Hymexazol as Aquatic Chronic 2, H411 : - Daphnia Mangna 21dEC10=0.4 mg/L : not rapidly degradable and EC10<1 mg/l ☐ Aquatic Chronic 2, H411 - Fish 96hLC50 >100 mg/l : not rapidly degradable + not meeting the bioaccumulation criteria + LC50>100 mg/L ☐ No classification				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
RAC agrees with the commenting MS and has additional remarks regarding the exposure periods in Lemna testing as a basis for an acute toxicity classification, and the validity of this specific Lemna study. The CLP guidance considers two guidelines as appropriate for testing *Lemna gibba*: OECD No. 221 and US-EPA 850.4400. The exposure period in both guidelines is 7 days. The CLP guidance indicates that the lemna test can last up to 14 days. In general, a 7-day exposure period is preferred for the purposes of determining an EC_{50} and a NOEC/EC_{10}. Extending test duration could lower test reliability as Lemna growth could unintentionally be inhibited, e.g. due to overcrowding and/or nutrient depletion, and test substance dissipation could lead to lower exposure levels. The CLP guidance does not discuss in detail the most appropriate exposure period for Lemna for the purpose of classification. Considering the prolonged test duration, RAC decided to check if this affected the validity of the test by calculating the doubling time of frond numbers of the control. This was determined to be 2.67 days, which exceeds the validity criterion of OECD TG 221 and US-EPA 850.4400, which state that the doubling time of frond numbers in the control must be less than 2.5 days. Data were not available to assess if the validity criterion was met after 7 days. Furthermore, outdated methodology (not based on growth rate) was used to derive the 14-day IC_{50} of 9.4 mg/L				

and concentrations were expressed as initial measured test concentrations. Thus based on the deviations, the study is considered less reliable (Klimisch score of 3). RAC recalculated the 14-day IC_{50} value using geometric mean measured test concentrations and followed the current methodology described in OECD TG 221 and US-EPA 850.4400, and obtained a 14-day IC_{50} of 28.2 mg/L. This value is just above the 48-hour EC_{50} of *Daphnia magna* of 28 mg/L, making Daphnia the most sensitive species to hymexazol. This does not affect the proposed classification.

PUBLIC ATTACHMENTS
1. Hymexazol_Fetal development position paper_confidential_sanitised.zip [Please refer to comment No. 6, 19]

CONFIDENTIAL ATTACHMENTS
1. Hymexazol_Fetal development position paper_confidential.zip [Please refer to comment No. 6, 19]