Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

1,2,4-triazole

EC Number: 206-022-9
CAS Number: 288-88-0

CLH-O-0000001412-86-270/F

Adopted

15 March 2019

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: 1,2,4-triazole
EC number: 206-022-9
CAS number: 288-88-0
Dossier submitter: Belgium

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
23.07.2018	Germany		MemberState	1
Comment received				
Concerning acute toxicity we recommend discussion and harmonization of an appropriate ATE.				
Dossier Submitter's Response				
Thank you for your comment. The proposed ATE was based on the lowest LD50.				
RAC's response				
Thank you. Your comment has been noted.				

Date	Country	Organisation	Type of Organisation	Comment number
03.08.2018	France		MemberState	2
Comment received				
FR: While not evaluated in this dossier, classification for eye irritation and STOT-RE (nervous system) may also be considered: - Serious eye damage/eye irritation page 10 While not evaluated in this dossier, based on available data, classification Eye irritant Category 2 H319 may be triggered. - Specific target organ toxicity-repeated exposure page 31 While not evaluated in this dossier, neuropathological findings most prominently cerebellar degeneration (Purkinje cell loss), decreased brain weight and altered FOB are observed in rats and mice in several studies (90-day, 2-generation, 1-year). Even if effective doses are above the threshold values for classification NOAEL for those effects are below the guidance values and in respect to the severity and the consistency				

of the neurotoxic effects observed throughout the database, a classification for STOT-RE cat.2 (nervous system) seems warranted.
Dossier Submitter's Response
Thank you for considering Eye irritation and STOT-RE. It was concluded in MSC-54 (Substance evaluation) that the best way forward was the urgent submission of a CLH dossier for reproductive toxicity (Repro 1B, H360 FD). Therefore Eye irritation and STOT were not evaluated in the CLH dossier.
RAC's response
Thank you. Your comment has been noted.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
03.08.2018	France		MemberState	3
Comment received				
FR: - Page 24-28: In the first embryotoxicity in rats (0, 100 and 200 mg/kg bw/day), the adjusted maternal body weight was not affected by treatment; the observed decreased bodyweight gain may be therefore more related to decreased number of foetuses and decreased fetal weight than to maternal toxicity. In the second one (0, 10, 30 and 100 mg/kg bw/day), the adjusted body weight is not reported. Decreased number of foetuses and decreased fetal weight observed at the top dose may also explained the decreased bodyweight gain of top dose dams. - The proposal for classification repr. 1B H360FD is supported.				
Dossier Submitter's Response				
Thanks for your support. Regarding the second study the uterus weight was not reported, thus the adjusted body weight is not available in the study.				
RAC's response				
Thank you. Your comment has been noted.				

Date	Country	Organisation	Type of Organisation	Comment number
23.07.2018	Germany		MemberState	4
Comment received				
Based on additional data, the proposal to modify classification for 1,2,4-triazole as Repro 1B, H360FD for adverse effects on sexual function, fertility and severe developmental effects in more than one species is supported. In a fertility study in rats for 1,2,4-triazole, an almost complete loss of fertility was observed in the highest dose group, as evidenced by a significantly reduced fertility index. In addition, in the highest dose group adverse effects on spermatogenesis and uterus dilatation were observed. Systemic toxicity was observed only to a small extent, so that it can be assumed that the reduction of fertility is due to the effect of 1,2,4-triazol. In a 90-day study in mice, also adverse effects on the spermatogenesis were found in highest dose group. Two oral developmental toxicity studies on 1,2,4-triazole in rats showed malformations such as cleft palate and microphthalmia in foetuses of the middle and high dose groups. Maternal toxicity for these effects is not considered relevant for evaluation.				

Due to the reduced fertility in both rat and mouse and the severe effects on fetal development in rats we consider a classification as Repr. 1B, H360FD as justified.
Dossier Submitter's Response
Thank you for your support.
RAC's response
Thank you. Your comment has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2018	Finland		MemberState	5
Comment received				

Fertility effects

In the 2-generation reproductive toxicity study in rats (Young A.D. and Sheets L.P., 2005, cited in JMPR 2008), almost complete infertility was observed at the highest dose in the P generation (fertility index: 76.7, 83.3, 86.2 and 7.1 % at 0, 250, 500 and 3000 ppm, respectively). There were only 2/28 animals with implants and the total number of implants were 265, 310, 279 and 3 respectively at 0, 250, 500 and 3000 ppm. A statistically significant higher number of total corpora lutea were noted at the highest dose level. Adverse effects on fertility are supported by other effects observed in this study that may have contributed to the infertility: increased incidence of uterus dilatation, reduction in epididymal sperm counts and reduction of normal sperm morphology percentage.

No mortality or clinical signs were observed during the study in the P generation. The adverse effects at highest dose level occurred together with other toxic effects (mild to moderate brain cerebellar degeneration/necrosis and effects on body weight in both sexes). Maternal body weight during gestation period was statistically significantly reduced at the highest dose but, however, could be explained by the low number of pregnant females (since 28 out of 30 dams were not pregnant).

The adverse effects on fertility seems to not be secondary non-specific consequences of systemic toxicity since maternal systemic toxicity is not high. In addition, lack of dose-dependence may be due to dose-spacing that deviates from the OECD 416 test guideline. The Finnish CA considers that classification 1,2,4 -triazole as Repr. 1B H360F is justified.

Developmental effects

In the developmental toxicity study in rats (Renhof 1988a, cited in JMPR 2008) increased incidence of cleft palates at the highest dose of 200 mg/bw/d was observed (0/253, 0/226 and 4/138 at 0, 100 and 200 mg/kg bw/d, respectively). The litter incidence was 12 % (3/25). Provided historical control data (1986-1989) indicate that the incidence is above the historical control data (one case cleft palate in the year 1987 with litter incidence 4.17% and one cleft palate in 1989 with litter incidence 7.69%). However, it is not clear from the CLH report if the performing laboratory was the same. Cleft palate is known to be rare in rats and a serious malformation.

The high rate of resorptions (53%) was observed at the highest dose level (may mask malformations). A significant increase of post-implantation losses at the highest dose level(number of implantation loss per dam: 0.5, 0.3 and 6.3 at 0, 100 and 200 mg/kg bw/d, respectively) and increase in the number of runts at 100 and 200 mg/kg bw/d were observed. Consequently, the mean number of foetus per dams was significantly

decreased. A significant dose-related decrease in mean foetus weight was seen at 100 and 200 mg/kg bw/d. According to the CLH report, in males, the incidence of undescended testicle was above the historical values (2/253, 11/226 and 6/138 at 0, 100 and 200 mg/kg, respectively). However, details of the historical control data are missing from the CLH report.

According to the CLH report no maternal mortality nor treatment related clinical signs were observed. A significant decrease in maternal body weight gain during pregnancy was reported at the highest dose level (96.9, 91.9 and 60.4 g at 0, 100 and 200 mg/kg bw/d, respectively). However, mean adjusted maternal body weight gains were increased at both dose levels during the pregnancy (30.8, 34.16 and 33.24 g at 0, 100 and 200 mg/kg bw/d, respectively). As the developmental effects were observed already at dose that was not toxic for the dams, all effects cannot be explained by the maternal toxicity. The adverse effects on development seems to not to be secondary non-specific consequences of systemic toxicity. If available, data from individual dams (i.e. body weight changes) with foetuses with cleft palate could clarify further the role of maternal toxicity. It seems that cleft palates cannot be explained by one of the impurities.

Overall, the Finnish CA considers that classification 1,2,4 -triazole as Repr. 1B H360D is justified.

Dossier Submitter's Response

Thanks for your support.
In the developmental toxicity study in rats (Renhof 1988a and b), the performing laboratory was the same. The historical control data were provided by this labo,

Renhof 1988a : In the study report, historical control data for spontaneous malformations are listed for the years 1984 and 1985. No cases of cleft palates were observed in these years.
Additional historical control data for spontaneous malformations from the same rat strain and test laboratory for the years 1983-1989 were provided. These data show one case of cleft palate in the year 1987 (litter incidence 4.17%) and one case of cleft palate in the year 1989 (litter incidence 7.69%).
Concerning the incidence of cryptorchidism, the incidence per litter of undescended testicle is also higher in the current study after exposure to 1,2,4-triazole (36.8 % at 100 mg/kg and 20 % at 200 mg/kg when the range of incidence is 0-12.5 % in the historical controls for the years 1983-1989).
Regarding individual data, 3 dams exposed to the highest dose (2065, 2096 and 2110) showed pups with cleft palate. The individual body weight data cannot explain this malformation.

Table 1 : Body weight (in g) and number of pups:

	Body weight				Number of living pups	Number of pups with cleft palate
	GD0	GD6	GD14	GD20		
Dam 2065	193	213	238	261	3	1
Dam 2096	197	215	236	270	8	1
Dam 2110	193	212	234	248	4	2
Mean for the highest dose level (200 mg/kg bw/d)	203.2	220.8	238.4	263.6	5.5**	
Mean for the control group	204.6	221.5	244.5	301.4	12.0	

RAC's response
Thank you. Your comment has been noted.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
23.07.2018	Germany		MemberState	6
Comment received				
Based on the provided information the LD50 value for oral toxicity of 1,2,4-Triazole is >500 and < 5000 mg/kg bw. Therefore, the proposal for classification as Acute Tox.4, H302 is supported.				
Dossier Submitter's Response				
Thanks for your support.				
RAC's response				
Thank you. Your comment has been noted.				

Date	Country	Organisation	Type of Organisation	Comment number
03.08.2018	France		MemberState	7
Comment received				
FR: Acute toxicity - oral route page 10 The proposal for classification Acute Tox. 4, H302 is supported.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you. Your comment has been noted.				