Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

propiconazole (ISO); (2*RS*,4*RS*;2*RS*,4*SR*)-1-{[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl}-1*H*-1,2,4-triazole

EC Number: 262-104-4
CAS Number: 60207-90-1

CLH-O-0000001412-86-139/F

Adopted
9 December 2016

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON PROPICONAZOLE (ISO); (2*RS*,4*RS*;2*RS*,4*SR*)-1-{[2-(2,4-DICHLOROPHENYL)-4-PROPYL-1,3-DIOXOLAN-2-YL]METHYL}-1*H*-1,2,4-TRIAZOLE

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: propiconazole (ISO); (2RS,4RS;2RS,4SR)-1-{[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl}-1H-1,2,4-triazole
EC number: 262-104-4
CAS number: 60207-90-1
Dossier submitter: Finland

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
13.05.2016	Germany		Member State	1
Comment received				
The German CA supports the proposed classification of propiconazole				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
12.04.2016	Belgium	Pesticide Action Network Europe	International NGO	2
Comment received				
These comments apply equally (except when noted) to propiconazole's HCL and its pesticide RAR, which we (PAN-E) are wondering when it will be released by EFSA. After searching the published toxicity literature (Medline via PubMed) with the search phrase "Propiconazole (toxic* OR hazard* OR risk*)" identifying cancer related published papers (a curated set (i.e. mostly the ones summed below) of 74 papers is available at: http://www.ncbi.nlm.nih.gov/sites/myncbi/anthony.tweedale.1/collections/49995514/public/). Generally, these findings have far less risk of bias, including insensitivity, than do industry's tox. studies, which this CLH/RAR nonetheless relies on. For both laws, this reality should be allowed in, to change the conclusion, per the slightly more specific following comments.				

Dossier Submitter's Response
Thank you for your comments. CLP classification is based on intrinsic properties of the substance which may cause physical, health and/or environmental hazards and trigger classification according to the criteria defined in the CLP Regulation. Studies which determine the properties should be conducted in accordance with the EU test methods (Regulation 440/2008) or in accordance with sound scientific principles that are internationally recognized or methods validated according to international procedures. In certain cases e.g. expert judgement and weight of evidence approach can be applied. We reviewed the published scientific literature prior to submission of the CLH proposal and the present classification proposal is based on studies which are considered adequate and reliable for the classification purposes. The comments concerning RAR are outside the scope of this public consultation.
RAC's response
Thank you for your comment. RAC agrees with DS's answer and support their opinion regarding the reliability of the studies used for classification of carcinogenicity.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2016	France		Member State	3
Comment received				
Page 53 : Results of the 2 year carcinogenicity study in mice are questionable. Indeed, exposure duration is too long for the species (a 18 month study is more appropriate for mice), and doses used are too high (highest dose exceeds the maximum tolerated dose). Incidence of hepatocellular adenoma observed in the 18 month study in mice were particular low in the concurrent controls while at the top dose, the incidence is slightly above the range of the laboratory control data. A lot of mechanistic studies show that hepatocellular proliferation seems to be primarily mediated by CAR receptor activation. This mode of action is generally considered as not relevant for human. In this case, specific data have been generated to support this conclusion. These are reasons why, France supports DS opinion.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
11.05.2016	Italy	Federchimica/Agrofarma	Industry or trade association	4
Comment received				
Federchimica/Agrofarma agrees that classification for carcinogenicity is not warranted. In addition to the arguments currently presented it should be noted that by using the				

available data and following a weight of the evidence assessment carried out according to the framework developed by the IPCS and ILSI/HESI (as discussed in Section 3.6.2.3.2 [sub-section k] of the Guidance on the Application of the CLP Criteria) it was demonstrated that: • Activation of CAR is required for propiconazole-induced hepatocellular tumorgenesis in mice. • Other known modes of action for hepatocellular tumorgenesis in rodents have been ruled out. • Based on extensive literature evidence and data generated for propiconazole, the CAR-mediated mode of action is not relevant to humans These points further support the proposal for no classification, based on lack of human relevance.
Dossier Submitter's Response
Thank you for your comments.
RAC's response
Thank you. Noted.

Date	Country	Organisation	Type of Organisation	Comment number
13.05.2016	Spain		Member State	5
Comment received				
Propiconazole promoted formation of spontaneously occurring tumours in one species (mice), in one tissue (liver), and in one sex (male). There are some factors (possibility of confounding effect of excessive toxicity, clearly exceeded maximum tolerated dose, reduced tumour latency, spontaneous tumours only at high doses, low incidence of adenomas statistically significantly increased only slightly above the contemporary historic control) that decrease the level of concern for human carcinogenicity. Besides, there is clear evidence that CAR receptor activation is involved in the tumorigenic action of propiconazole in CD-1 mice. Although it remains equivocal whether this mechanism is the only motivator, recent studies in CAR-null mice with other triazoles (cyproconazole, fluconazole, tebuconazole) suggest that CAR-activation is required for propiconazole-induced tumorigenesis. As said in propiconazole CLH report, a gene expression biomarker signature assessment comparing effects in wild-type and CAR-null mice showed that propiconazole increases liver weights and hepatocyte proliferation in a CAR-dependent manner (Oshida et al. 2015). Since the liver responses to propiconazole are very similar to those induced by cyproconazole (CLH-dossier of cyproconazole), these findings on CAR-null mice suggest that CAR-activation has a prime role as a mediator for propiconazole-induced tumourgenesis. The Committee for Risk Assessment in its opinion, adopted in 11 September 2015, concluded not to classify cyproconozale for its carcinogenicity effects. In conclusion, there is clear evidence that CAR receptor activation is involved in tumorigenic action of propiconazole in CD-1 mice. Therefore, it is considered that, the data available do not support a classification for carcinogenicity for propiconazole.				
Dossier Submitter's Response				
Thank you for your support.				

RAC's response
Thank you. Noted.

Date	Country	Organisation	Type of Organisation	Comment number
13.05.2016	Germany		Member State	6
Comment received				
Propiconazole promoted formation of spontaneously occurring tumours in the liver of male mice. However, excessive toxicity and spontaneous tumours only at high doses decrease the level of concern for human carcinogenicity. Furthermore, there is evidence that CAR receptor activation is involved in tumorigenic action of propiconazole in CD-1 mice (4.9.4). Therefore the proposal of the dossier submitter not to classify is supported (4.9.6).				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
12.04.2016	Belgium	Pesticide Action Network Europe	International NGO	7
Comment received				
the CLH/RAR: - is missing 19 of 32 published findings of cancer (incl. mechanistic); - dismisses the 13 remaining published papers as mutagenic-mechanism, while propiconazole's very limited carcinogenesis is not via mutagenesis (see below why this is wrong); - makes the only industry test that caused significant rate of liver cancers disappear by apparent post hoc fraudulent magically elevated rate of cancers in the neg. control mice– i.e. why did those non-exposed cancers not show up in the original neg. controls, under the exact same conditions? There is no information on whether this sudden new arm of the experiment was TG=GLP compliant with the original GLP plan for the experiment, so I have submitted a complaint of suspected GLP fraud to Finland's GLP enforcement agency. In sum, it is impossible for the CLH/RAR to credibly make its conclusion about carcinogenicity without evaluating all this published evidence that it is a liver and possibly other carcinogen via mutagenic and metabolic (related to its fungicidal mode of action) paths. As always, industry, RMS, EFSA & EChA are swimming against a tide of far more reliable, opposite, findings. I mean, these authors are so sure that they call it a known carcinogen in the title of some of these published findings!				
Dossier Submitter's Response				
Thank you for your comments. Statistically significantly increased incidence of hepatocellular adenomas in propiconazole treated male mice compared to concurrent controls was observed in <u>two</u> studies. Namely,				

in a two year carcinogenicity study in mice (**21% and 40%** incidence of adenomas in control and at 2500 ppm, respectively, DAR IIA 5.5/03-04) and in a 18 month carcinogenicity study in male mice (**2% and 20%**, incidence of adenomas in control and at 850 ppm, respectively, DAR IIA 5.5/05). In the former study slightly increased incidence of hepatocellular carcinomas was also observed in high dosed (2500 ppm) males compared to concurrent controls at the end of the study. After the aforementioned studies a 18 month reference study was conducted in the same laboratory in order to collect control data on the spontaneous occurrence of these tumours in CD-1 mice. In this study the incidence of hepatocellular adenoma in males ranged **6-18%**, whereas the notifier had previously submitted historical control data from another laboratory with an incidence of **6-18.4%**. Thus, the new reference data did not change the outcome of the study: incidence of liver adenomas in propiconazole treated males was statistically significantly increased compared to concurrent controls and slightly above the contemporary historical control range. Our proposal not to classify propiconazole for carcinogenicity is based on the following factors that decrease the concern for human carcinogenicity according to CLP criteria: tumors were found in one species and in males only; malignant tumors (carcinomas) were observed only at a dose level clearly exceeding the maximum tolerated dose (possibility of confounding effect of excessive toxicity) at the end of the normal lifespan of mice (decreased tumor latency); and propiconazole promoted formation of spontaneously occurring tumors only at high doses.

Regarding your suspection of GLP fraud, we have consulted the Finnish GLP authorities EFSA, ECHA and the EU Commission. According to the information from the GLP authority of the country where the testing laboratory is based, the laboratory conducting the 18-month mouse carcinogenicity study was in their GLP monitoring program in the period of 1997-1999. The test facilities were GLP compliant in the area of expertise "long term toxicology". The laboratory was inspected in 1996 and 1998. "Short and long term toxicology" was inspected however not this particular mouse study. We thoroughly discussed whether conducting a new separate reference study after carcinogenicity study is acceptable. As an outcome from those discussions we concluded that the new reference data did not change the outcome of the study and does not affect our proposal. Based on this and on the facts mentioned above we did not consider it necessary to request a study audit.

We have reviewed both of the studies conducted on the request of regulatory authorities and studies published in the open scientific literature (all reviewed studies are not referred in the CLH report). There are no in vivo animal studies showing tumor profile that would differ (i.e. being more severe) from that described in the CLH report. The notifier has not conducted epidemiological studies on humans. In the public literature there are no studies indicating health effects on the general population due to exposure to propiconazole.

We did not evaluate the germ cell mutagenicity endpoint. The data on mutagenicity is included in the CLH report only as supporting evidence for the carcinogenicity endpoint, e.g. for evaluation of carcinogenicity MoA. No evidence of mutagenicity has been observed in the in vitro and in vivo mutagenicity assays (section 4.8., Table 20) submitted by the notifier. This suggests that propiconazole is not genotoxic.

The notifier has submitted a report of human relevance framework assessment for carcinogenicity MoA of propiconazole. The report solely represents their view. We have reviewed the submitted studies, the MoA report and the open literature (p.79). Our conclusion is that it remains equivocal whether CAR-activation is the only motivator for

propiconazole induced tumorgenesis, but the recent studies in CAR-null mice suggest that CAR-activation is required for propiconazole-induced hepatocellular tumourgenesis in mice.
You refer to studies by Ross et al (2009, 2010 and 2012) on mutagenicity of propiconazole, and to the Ross and Leavitt (2012) response to commentary by Shane et al (2012) in the Environmental and Molecular Mutagenesis journal (comment number 10). We have not included these references in the CLH report but two of these studies (Ross et al 2009 and 2010) are included in the MoA human relevance framework assessment of the notifier. It is notable that in their response to commentary Ross and Leavitt (2012) stated that they do not consider propiconazole to act via a genotoxic/mutagenic MoA but the increase in mutation frequence in the liver as a consequence of oxidative stress is one element of the complex MoA.

In the case RAC considers that the data on carcinogenicity warrants classification, the MoA data for carcinogenicity and MoA´s relevance for humans will be evaluated. We are of the opinion that this additional data should be taken into account at that stage.

Please see also our response to comment number 2 for published scientific articles on propiconazole.

Ross JA and Leavitt S (2012). Response to commentary: Re-evaluation of the Big Blue® mouse assay of propiconazole suggests lack of mutagenicity. Environ. Mol. Mutagen Aug;53(7):574-7.

Ross JA et al (2012): Quantitative changes in endogenous DNA adducts correlate with conazole in vivo mutagenicity and tumorigenicity. Mutagenesis vol. 27 no. 5 pp. 541–549, 2012

RAC's response

RAC supports the DS's answer. There is no doubt about the carcinogenic potential of propiconazole for mice. However, the CLP Regulation is established for protecting humans and there are several mechanistic studies that notably diminish the relevance for humans of the carcinogenicity found in mice. Regarding the suspicion of GLP fraud RAC considers, after the validation performed by the DS, that there are no reasons to doubt the reliability of the mice studies. RAC, as in the case of answer to comment number 2, also supports the DS's opinion regarding the reliability of the studies used for assessing carcinogenicity for classification purposes.

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2016	Switzerland	Syngenta (on behalf of the Propiconazole Task Force)	Company-Manufacturer	8

Comment received

Reference CLH Report Section 4.9 carcinogenicity (pg54 to 82). Syngenta (on behalf of the Propiconazole Task Force) agrees that classification for carcinogenicity is not warranted.

In addition to the arguments currently presented in the CLH report it should be noted that by using the available data and following a weight of the evidence assessment carried out according to the framework developed by the IPCS and ILSI/HESI (as discussed in Section 3.6.2.3.2 [sub-section k] of the Guidance on the Application of the CLP Criteria) it

was demonstrated that: • Activation of CAR is required for propiconazole-induced hepatocellular tumorgenesis in mice. • Other known modes of action for hepatocellular tumorgenesis in rodents have been ruled out. • Based on extensive literature evidence and data generated for propiconazole, the CAR-mediated mode of action is not relevant to humans These points further support the proposal for no classification, based on lack of human relevance.
Dossier Submitter's Response
Thank you for your comments. Your report of human relevance framework assessment in its original form is provided as an attachment to section 13 of the CLH dossier and the summary of the report as Annex 8 of the CLH report.
RAC's response
Thank you. Noted.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
13.05.2016	Germany		Member State	9
Comment received				
It is supported to propose no classification, because no evidence of mutagenicity of propiconazole was observed (4.8.2).				
Dossier Submitter's Response				
The data on mutagenicity was included in the report only as supporting evidence for the carcinogenicity endpoint, we did not evaluate the mutagenicity endpoint. Unfortunately, the endpoint germ cell mutagenicity was opened for comments in public consultation by mistake, which was later corrected by ECHA.				
RAC's response				
Thank you. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
12.04.2016	Belgium	Pesticide Action Network Europe	International NGO	10
Comment received				
I agree with you accepting comment on mutagenicity even though the proposal is not for such a C&L listing; apparently you agree with my view that mutagenicity is in this case a carcinogencity mechanism? - The CLH/RMS proposal missed 2 of 5 published mutagenicity findings from academia. A couple dozen of the mostly missed published cancer studies, including the ones investigating mutagenicity, conclude that liver & other cancer is caused by many alterations cells, including mutagenicity (many of these published authors are from US				

EPA labs, but total of about five labs broadly confirm this). One of these cancer & mutagenicity findings is dismissed by citing a published paper from industry consultants that dismisses one of the USEPA lab findings…conveniently neglecting (i.e. missed) the original author's detailed (4 page) final published rebuttal (Ross & Leavitt '09)!! This blatant carelessness action was prompted by the industry, I would guess.
Dossier Submitter's Response
The data on mutagenicity was included in the report only as supporting evidence for the carcinogenicity endpoint, we did not evaluate the mutagenicity endpoint. Unfortunately, the endpoint germ cell mutagenicity was opened for comments in public consultation by mistake, which was later corrected by ECHA. Please see also our response to comment number 7.
RAC's response
Please, see RAC's answer to comment number 7.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
16.05.2016	Sweden		Member State	11
Comment received				
The SE CA agree that the increased incidence of cleft palates in rats treated with propiconazole justifies classification for developmental toxicity. However, since there is no convincing evidence demonstrating that the sensitivity of humans is more similar to rabbits than rats we do not agree that the concern for developmental toxicity is reduced by observations being made only in one species. Neither do we agree that the concern is reduced by the high maternal toxicity indicated by mortality (less than 10%), clinical signs and body weight gain since we do not consider such toxicity likely to result in a malformation such as cleft palate. The incidences of cleft palate observed in the two foetuses occur in different litters. Moreover, it cannot be excluded that some additional cases may be masked by the slightly increased post implantation loss and reduced number of viable foetuses in the supplementary developmental rat study. Since this rare malformation is commonly observed with other "conazoles" the findings are not considered to appear by chance thus the low frequency seems to rather reflect a low potency compared to other "conazoles". Since potency is not considered when assigning classification category for reproductive toxicity (only for specific concentration limits), we believe it needs to be further discussed whether or not criteria for category 1B are fulfilled, rather than category 2 as proposed.				
Dossier Submitter's Response				
Thank you for your comments. We agree that it is unlikely that cleft palates observed in two developmental toxicity studies are of spontaneous origin or a consequence of maternal toxicity. In addition, we agree that it is not known whether sensitivity of humans is more similar to rat or rabbit and that potency is not criteria for reproductive toxicity classification. RAC will further consider whether criteria for category 2 or 1B are fulfilled.				

RAC's response
Thank you. Noted.

Date	Country	Organisation	Type of Organisation	Comment number
13.05.2016	Spain		Member State	12

Comment received

Propiconazole caused malformations (cleft palate, cleft lip) and embryo/fetal toxicity (increased post implantation loss) in rats at maternally toxic dose (reduced maternal body weight gain and severe clinical signs of toxicity) Increased incidence of cleft palates in rats has also been observed in response to other triazoles (e.g. cyproconazole and epoxiconazole).

In rats, also significantly increased incidence of skeletal variations (rudimentary ribs and non-ossified sternebrae) and an increased incidence of urinary tract variations occurred in association with maternal toxicity, and thus they may represent a delay in growth and development secondary to maternal toxicity.

In a rabbit propiconazole caused marked maternal toxicity at the highest dose, increased incidences of resorptions, abortions and early deliveries and an increased incidence of a variation, a fully formed 13th rib in fetuses. The increased incidence of fully formed 13th rib is a variation and occurred only at the highest dose in association with marked maternal toxicity, and may therefore be a secondary consequence of maternal toxicity.

A number of compounds in the triazole group appear to have a common intrinsic teratogenic activity. The mechanism of the teratogenic effect has been hypothesized to be related to the capability of these substances to alter embryonic retinoic acid catabolism. Retinoid acid is a well-known morphogen in vertebrate and invertebrate embryos. Triazole-related abnormalities are confined to structures controlled by retinoic acid, especially the neural crest cells, hind brain, cranial nerves, and craniofacial structures.

An important role of some CYP isoforms (CYP26 isoforms) expressed during mammalian development is the catabolism of retinoic acid. The suggested mechanism for the teratogenic effects involves the inhibition of CYP 26, which means increased concentrations of retinoic acid (Menegola et al., 2006).

Besides, the interference with key enzymes involved in steroid hormone synthesis and the aromatase (CYP19) inhibition disturb the balance between estrogens and androgens and thus may potentially affect embryonic development. Post-implantation losses and resorptions could be secondary to endocrine disruptive effects of aromatase inhibition in the dams.

The specificity and the spontaneous infrequence of some malformations (i.e cleft palate) otherwise commonly seen with triazoles, indicates that they cannot be considered secondary to maternal toxicity. Besides, there is no information showing that the mechanism is not relevant for humans.

However, there are some additional considerations that decrease the level of concern for developmental hazard:

- A low incidence of cleft palate was observed in both rat studies
- Cleft palate were not observed in rabbit

• The incidence of cleft palate and post implantation lost, were both in presence of maternal toxicity Therefore, from the data available, we support the dossier submitter opinion than a classification as Repr. 2; H361d is more appropriate for propiconazole. Regarding fertility, we consider not classification.
Dossier Submitter's Response
Thank you for your support.
RAC's response
Thank you. Noted.

Date	Country	Organisation	Type of Organisation	Comment number
13.05.2016	Germany		Member State	13
Comment received				
Classification as Repr. 2; H361d is supported based on the low incidences of cleft palates in the two rat studies.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
13.05.2016	Denmark		Member State	14
Comment received				
We agree with RMS that propiconazole should have a classification as category 2 for reproductive toxicity (development) based on the increased incidence of cleft palate. Furthermore, the effects on estrus cycle and AGD in females are also a concern and a classification for effects on fertility should be applied in addition to effects on development.				
Dossier Submitter's Response				
Thank you for your support. We agree that there are findings in the open scientific literature which add concern for reproductive toxicity of propiconazole (for details see section 4.10.3 of the CLH report). In Rockett et al (2006) exposure to high doses of propiconazole (500 and 2500 ppm) from gestation day 6 until PND98 resulted disrupted oestrus cyclicity in female pups on first two weeks after vaginal opening. The oestrus cyclicity was normalized in both groups in later assesments on weeks 5-6 and 9-10 after vaginal opening. Histology of the ovaries, body weight on PND0 and anogenital distance on PND0 were unaffected by the treatment. Goetz et al (2007) reported increased AGD in male rat pups on PND0 following exposure to 2500 ppm (144-174 mg/kg/d) propiconazole in diet from gestation day 6 until PND120. Testes weights were increased on PND50 at 500 ppm (53 mg/kg/d) and on PND22 at 2500 ppm. Serum testosterone levels were increased at PND92 at 500 ppm and 2500 ppm. There were no treatment related effect on the day of preputial separation, histology				

of the pituitary, thyroid, testis, epididymis or ventral prostate, or sperm morphology and motility.
Increased serum testosterone levels and serum 17alfa-hydroxyprogesterone levels in dams in association with increased foetal weights following propiconazole treatment (50 mg/kg/day from gestation days 7-21) have been reported by Taxvig et al (2008). Lately Costa et al. (2015) reported significant increase in abnormal sperm tail morphology, inceased seminal vesicle and vas deferens weight, and decreased serum estradiol levels in male rats following treatment with 4 mg/kg/day propiconazole from PND50 to 120. There were no effects on other sperm parameters or morphometric parameters of the testis. The higher propiconazole dose used in the study, 20 mg/kg/day impaired sexual behaviour of males but no other treatment-related effects were observed.

These effects are consistent with the proposed ED MoA of propiconazole (interference with steroidogenesis). However, we chosed not to propose classification for fertility for propiconazole because of the following reasons:

i) there were no significant effects on fertility, fecundity or reproduction parameters in a two-generation reproduction study (DAR IIA 5.6.1/01) or when assessed, in studies published in open scientific literature (see 4.10.3.)
ii) increase of AGD in male pups and reversible disruption of oestrus cycle may rather contribute to classification for developmental toxicity (reproductive development) than for fertility
iii) although all these effects suggest for disturbed steroidogenesis they may be considered as individual findings. When assessed, effects on AGD or oestrus cycle have not been observed in other studies. Effects on sperm parameters, when assessed, have not been observed in studies other than Costa et al (2005). However, it is notable that exceptionally low propiconazole dose (4 mg/kg/d) was used by Costa et al (2005).

RAC's response

RAC supports the DS's answer. The reported effects do not have enough consistency, severity and reproducibility to warrant classification for fertility.

Date	Country	Organisation	Type of Organisation	Comment number
13.05.2016	Belgium		Member State	15

Comment received

Based on the available data, a slight increase incidence of cleft palate has been observed :
o 0.33% at 90mg/kg bw/d and 0.7% at 300/360mg/kg bw/d (DAR IIA 5.6.2/01)
o 0.097% at 300mg/kg bw/d (DAR IIA 5.6.2/02)
These results were not in the historical control data range (0-0.016%) and were observed at dose levels which did not induced severe maternal toxicity effects (except at 300-360mg/kg bw/d). In the DAR IIA 5.6.2/01 study, the reduced body weight gain was only observed during GD6-8 and was not modified at the end of the study. The high dose level induced toxic effects (ataxia, lethargy, ..) however these effects were not observed at 90mg/kg bw/d.
The dossier submitter mentioned that "increased incidence of cleft palates in rat has also been observed in response to exposure to other triazoles". BE CA would have appreciated more details about the substances (read across) and the studies which showed the cleft palate.

Dossier Submitter's Response
Thank you for your comments. RAC has previously made opinions on several triazoles. We did not consider necessary to include detailed comparison of these substances in the CLH report since this information is already documented in these opinions.
RAC's response
Thank you for your comments. RAC supports the DS's answer because the available information is enough by itself for establishing classification without the need for read-across.

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2016	Switzerland	Syngenta (on behalf of the Propiconazole Task Force)	Company-Manufacturer	16

Comment received

Reference CLH Report Section 4.10.2 Developmental toxicity (pg89 to 102). In a weight of evidence evaluation of propiconazole for developmental toxicity the following can be confirmed:

- No treatment related effect on embryolethality (resorption/postimplantation loss, reductions in number of live fetuses)
- Structural abnormalities were limited to low incidences of cleft palate in the rat, the incidences were considered to be within HCD for the strain of rat
- There was no evidence of effects induced by propiconazole administration to dams which would result in functional deficiency of foetuses

In addition, pregnancy (abortions in rabbits) and foetal differences from controls (in rats delays in ossification, urogenital tract development delays, rudimentary ribs and fully formed 13th ribs in rabbits) were considered related to altered growth (delayed development) and were only observed in the presence of severe or marked maternal toxicity. On the basis that cleft palate is considered of spontaneous etiology and other effects are considered secondary to marked maternal toxicity there is no convincing evidence that propiconazole displays a developmental hazard and should not be classified as Repr. 2 H361. Additional information are provided in the document attached "Final Propiconazole Syngenta Public Comments Developmental Toxicity 2016.docx".

ECHA note - The following attachment was submitted with the comment above:
Final Propiconazole Syngenta Public Comments Developmental Toxicity 2016.docx

Dossier Submitter's Response

Thank you for your comments. We disagree with your view that the data on propiconazole is insufficient for Repr. 2: H361d classification. Our proposal to classify propiconazole for developmental toxicity is primarily based on low incidences of cleft palates observed in two rat developmental toxicity studies (DAR IIA 5.6.2/01 and 5.6.2/02). As you acknowledge, cleft palate is a rare malformation in rat. No cleft palates had occurred in the laboratory that conducted the rat developmental toxicity studies (incidence **0/5431** foetuses in 19 studies during 1983-1985). This data is the most relevant historical control data, i.e. the data from the same laboratory within five years time frame to study. Thus, the incidences of cleft palates in response to propiconazole treatment (**1/302; 0.33%, 2/285; 0.7%** and **2/2064; 0.097%**) in rat developmental toxicity studies are higher than HCD range. Cleft palates occurred in different litters (3 cases in three different litters and two cases in two different litters) so they are unlikely to be of genetic origin. The

incidence of cleft palates was lower in the supplementary developmental toxicity study but this does not overrule other factors listed here and the fact that no cleft palates occurred in concurrent controls in ether study or in HCD of the conducting laboratory. Moreover, slightly increased post-implantation loss and reduced number of viable foetuses may have masked additional cleft palate cases in the supplementary study. Maternal toxicity was marked at high dose in both studies but one cleft palate occurred also at an intermediate dose (90 mg/kg/d) in association with only moderate maternal toxicity. In addition, cleft palates are unlikely to occur as a secondary consequence of maternal toxicity. Cleft palates are commonly observed in response to triazoles. Alltogether, it is unlikely that cleft palates occurred spontaneously in propiconazole treated groups in the two rat developmental toxicity studies.

Cleft palate severely impairs nursing of neonate and later eating (in humans also speech and hearing problems may occur), thus it is a functional deficiency.

You submitted summary of a third rat developmental toxicity study (Fritz 1979) in public consultation. We have not received this study earlier for either PPP or Biocide approval processes. The study is conducted prior to regulatory test guidelines and implementation of GLP. The main deviation from the TG OECD 414 is stated to be the dosing window (gestation days 6 to 15), but on the basis of the study summary there are also other deviations, e.g. clinical signs of toxicity were not recorded. We are not able to fully evaluate the acceptability of this study for classification according to CLP on the basis of study summary and due to short time frame. The full study report of the study has now been submitted to RAC for their decision making. Regardless of whether the study is accepted or not, we are of the opinion that negative findings of this study do not overrule the findings of other developmental toxicity studies.

RAC's response

RAC supports the DS's answer. The incidence of cleft palate together with other evidence of developmental toxicity warrants classification and even in the case of some new negative studies the already available studies (two in rat and one in rabbit) should not be ruled out.

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2016	France		Member State	17

Comment received

P99:
A table summarizing the results of the available studies exploring endocrine disrupter effects would have helped to perform a weight of evidence analysis.
Furthermore since propiconazole was one of the substances included in the Endocrine Disruptor Screening Program Tier 1, several other studies on endocrine properties are available.

P103
France agrees that propiconazole should be classified for developmental toxicity.
However, the category should be more discussed, considering the manifestations of developmental toxicity:
- Malformations in rat including cleft palates (malformation implying a disturbance in the process of craniofacial morphogenesis commonly observed with triazoles) observed in the two developmental toxicity studies and craniofacial malformations also observed in the 2-generation study
- Death of the developing organism in the developmental toxicity study in rabbit,

characterised by an increased incidence of resorptions and abortions.
Dossier Submitter's Response
Thank you for your comments. Endocrine disrupter status of substances is not in the scope of CLH process. Thus, only studies which have examined potential adverse effects of propiconazole on fertility, reproduction or development were reviewed in the CLH report (4.10.3.). All studies solely examining an ED mechanism (e.g. receptor binding assays) are not included in the report. Propiconazole was included in the Endocrine Disruptor Screening Program Tier 1 of U.S Environmental Protection Agency. The in vivo studies on fertility and reproduction used in the Weight of analysis report of this program for propiconazole have been included in the CLH report. https://www.epa.gov/ingredients-used-pesticide-products/weight-evidence-edsp-propiconazole We agree that RAC should further consider whether the criteria for category 2 or 1B (developmental toxicity) are fulfilled for propiconazole. Please see also our response to comment 11.
RAC's response
Thank you. RAC agrees with the DS that a specific assessment of endocrine disruption is not needed since this hazard is not included under CLP regulation.

Date	Country	Organisation	Type of Organisation	Comment number
11.05.2016	Italy	Federchimica/Agrofarma	Industry or trade association	18
Comment received				
In a weight of evidence evaluation of propiconazole for developmental toxicity the following can be confirmed: • No treatment related effect on embryo lethality (resorption/post implantation loss, reductions in number of live foetuses) • Structural abnormalities were limited to low incidences of cleft palate in the rat, the incidences were considered to be within HCD for the strain of rat • There was no evidence of effects induced by propiconazole administration to dams which would result in functional deficiency In addition, pregnancy (abortions in rabbits) and foetal differences from controls (in rats delays in ossification, urogenital tract development delays, rudimentary ribs and fully formed 13th ribs in rabbits) were considered related to altered growth (delayed development) and were only observed in the presence of severe or marked maternal toxicity. On the basis that cleft palate is considered of spontaneous etiology and other effects are considered secondary to marked maternal toxicity there is no convincing evidence that propiconazole displays a developmental hazard and should not be classified as Repr. 2 H361d.				
Dossier Submitter's Response				
Thank you for your comments. We disagree with your view on non classification. Please see our response to comment 16.				
RAC's response				
Thank you. RAC supports the DS's opinion and consider that propiconazole warrants classification.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON PROPICONAZOLE (ISO); (2*RS*,4*RS*;2*RS*,4*SR*)-1-{[2-(2,4-DICHLOROPHENYL)-4-PROPYL-1,3-DIOXOLAN-2-YL]METHYL}-1*H*-1,2,4-TRIAZOLE

Date	Country	Organisation	Type of Organisation	Comment number
12.04.2016	Belgium	Pesticide Action Network Europe	International NGO	19
Comment received				
The CLH/RMS proposal missed 2 of 4 published reprotox studies. It concludes: "In conclusion, the above reviewed in vivo studies revealed no major effects of propiconazole on fertility or reproduction. The reported increases in serum testosterone, pup weights, testes weights, and in anogenital distance are consistent with the proposed ED MoA of propiconazole (interference with steroidogenesis). In addition, abnormal sperm tail morphology after exposure to low dose and impaired sexual behaviour and disrupted oestrus cycle following mid and high doses of propiconazole were reported (Rockett et al 2006, Costa et al 2015). However, taken into account the partial controversy of the findings between studies, and the obtained negative results on fertility and reproduction, their biological significance is presently obscure." What "partial controversy...between studies"? The proposal has ignored 12 of the 16 published findings (including ecotox) on endocrine disruption, most concerning reprotox. As the proposal says, propiconazole's mode of action is to disrupt steroid hormone genesis, and this is also reflected in the missed published literature … in short, the independent academia's findings are strong on reprotox & ED endpoints, including the wrongly-missed & dismissed lo-dose findings. Clearly propiconazole is a more potent, i.e. Class 1, reprotox agent.				
Dossier Submitter's Response				
Thank you for your comments. Please see our responses to comments 11, 14 and 17 for the proposed reproduction toxicity classification. Please see our response to comments 2 and 32 for the references included in the CLH report.				
RAC's response				
Thank you. RAC supports the DS's answer.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2016	France		Member State	20
Comment received				
LD 50 for males and females should be established separately and the lower LD50 should be taken into account. Thereby the acute oral LD50 of propiconazole should be 1138 mg/ kg bw/ d. Nevertheless, France agrees with the classification proposed by Finland namely Acute Oral Toxicity; H302 Harmful if swallowed.				
Dossier Submitter's Response				
Thank you for your comment. The lowest oral LD50 value is 550 mg/kg bw. This value is from the OECD 425 study in female rats (dRAR B.6.2.1.3). The study is also considered key study, which unfortunately is not stated in the CLH report.				
RAC's response				
Thank you. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
13.05.2016	Spain		Member State	21
Comment received				
In the oral toxicity studies, the lowest LD50 was 227 mg/kg bw, therefore propiconazole should be classified as Acute Acute Tox 4, H302: Harmful if swallowed, because LD50 is within the limits 300< ATE ≤ 2000 (oral, mg/kg bw). The minimum classification Acute tox. 4* should be considered confirmed.				
Dossier Submitter's Response				
Thank you for your comment. The lowest oral LD50 is 550 mg/kg bw. This value is from the OECD 425 study in female rats (dRAR B.6.2.1.3). The study is also considered key study, which unfortunately is not stated in the CLH report.				
RAC's response				
Thank you. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
13.05.2016	Germany		Member State	22
Comment received				
The existing classification for acute oral toxicity, Acute Tox. 4; H302, is supported (4.2.5).				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
13.05.2016	Belgium		Member State	23
Comment received				
The BE CA supports the proposed classification as Acute tox. 4				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you. Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2016	Italy	Istituto Superiore di Sanità	National Authority	24
Comment received				
In the CLH dossier is not evaluated the sections of skin corrosion/irritation and serious eye damage/eye irritation. Should be considered, for this endpoints, the assessment in the report of FAO: FAO Plant Production and Protection Paper, 178, 2004 - Pesticide residues in food - 2004. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and WHO the Core Assessment Group				

Dossier Submitter's Response
Thank you for your comment. We have not evaluated the endpoints skin corrosion/irritation and serious eye damage/eye irritation.
RAC's response
RAC can issue opinions only for hazards that have been reviewed by the DS. Therefore, RAC did not discuss this hazard.

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2016	Italy	Istituto Superiore di Sanità	National Authority	25
Comment received				
In the CLH dossier is not evaluated the sections of skin corrosion/irritation and serious eye damage/eye irritation. Should be considered, for this endpoints, the assessment in the report of FAO: FAO Plant Production and Protection Paper, 178, 2004 - Pesticide residues in food - 2004. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and WHO the Core Assessment Group				
Dossier Submitter's Response				
Thank you for your comment. We have not evaluated the endpoints skin corrosion/irritation and serious eye damage/eye irritation.				
RAC's response				
RAC can issue opinions only for hazards that have been reviewed by the DS. Therefore, RAC did not discuss this hazard.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
13.05.2016	Spain		Member State	26
Comment received				
We agree with the dossier submitter that classification as skin Sens.1; H317 should be retained.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
13.05.2016	Germany		Member State	27
Comment received				
The existing classification Skin Sens. 1; H317 is supported (4.6.1.4).				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you. Noted.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON PROPICONAZOLE (ISO); (2*RS*,4*RS*;2*RS*,4*SR*)-1-{[2-(2,4-DICHLOROPHENYL)-4-PROPYL-1,3-DIOXOLAN-2-YL]METHYL}-1*H*-1,2,4-TRIAZOLE

Date	Country	Organisation	Type of Organisation	Comment number
13.05.2016	Belgium		Member State	28
Comment received				
The BE CA supports the proposed classification as Skin sens. 1.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2016	Switzerland	Syngenta (on behalf of the Propiconazole Task Force)	Company-Manufacturer	29
Comment received				
Reference CLH Report Section 4.6.1 skin sensitisation (pg 31 to 35). A classification for skin sensitisation category 1 (H317) is considered appropriate by Syngenta, however, based on new data propiconazole can be classified into subcategory 1B. Propiconazole is currently classified for skin sensitization (R43) (Annex of EU Dir 67/548 (29th ATP)). In the submitted study, the response was 50% at a 5% intradermal induction dose; however, an additional study has been provided in which there was no response at a 1% intradermal dose. Therefore, sub-category 1A can be excluded on the basis that there was no evidence (0% response) at an intradermal induction dose of propiconazole of 1% and the classification should be Skin Sens. 1B; H317. New data are provided in the document attached "Final Propiconazole Syngenta Public Comments skin sensitisation 2016.docx". ECHA note - The following attachment was submitted with the comment above: *Final Propiconazole Syngenta Public Comments skin sensitisation 2016.docx*				
Dossier Submitter's Response				
Thank you for your comment. New data provided is a guinea pig study conducted according to old OECD guideline 406. In the induction phase skin reactions observed in control animals were similar to the test animals. 24 h after the challenge, one control animal (that received only vehicle) showed significant dermal response. Other animals did not have significant response. Because of the non-specific positive reactions in vehicle control animals, the study is considered not acceptable and cannot be taken into account for classification. Thus, we consider the new study not acceptable and the current classification Skin Sens. 1; H317 should be retained because the data do not allow subcategorization.				
RAC's response				
Thank you. RAC supports the DS's answer. RAC also noted that no positive controls were included in the new study and therefore negative results might be interpreted as an intrinsic resistance of the animals to sensitisation.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
13.05.2016	Germany		Member State	30
Comment received				
The severity of hepatocellular necrosis was only very slight to moderate and the necrosis appeared to subside with time. Therefore the proposal of the dossier submitter not to classify is supported (4.7.6).				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you. Noted.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2016	France		Member State	31
Comment received				
We agree with the classification and M factors proposed for Environmental hazards.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for the comment.				

Date	Country	Organisation	Type of Organisation	Comment number
12.04.2016	Belgium	PAN-Europe	International NGO	32
Comment received				
In the Medline search linked in my previous comment, the CLH proposal missed all of 5 published findings of synergistic toxicity, usually in an aquatic environment.				
Dossier Submitter's Response				
Thank you for your comment. CLP classification is based on intrinsic properties of the substance which cause physical, health and/or environmental hazards and trigger the classification according to the criteria defined in the CLP Regulation. Synergistic toxicity is therefore out of the scope of harmonized CLP classification. Studies which determine the properties should be conducted in accordance with the EU test methods (Regulation 440/2008)38 or in accordance with sound scientific principles that are internationally recognized or methods validated according to international procedures. In certain cases e.g. expert judgement and weight of evidence approach can be applied. The present classification proposal is based on studies which are considered adequate and reliable for the classification purpose. In order to take the published findings into account there should be enough information to evaluate the studies starting with specifying the studies and endpoints that would be relevant for classification. Links to the published information are not enough.				
RAC's response				
Thank you for the comment. Following public consultation, additional information was provided highlighting synergistic effects and potential endocrine disruption effects in fish. RAC evaluated this additional information. However, RAC notes that this new information				

is not considered sufficiently adverse and does not change the classification proposed by the DS.

The most relevant study, Skolness *et al*. (2013) showed long-term effects and potential endocrine activity of propiconazole on fish after 21 days of exposure conditions similar to the OECD TG 229 test. Regarding endocrine effects, propiconazole significantly increased the production of plasma VTG (at 50 µg propiconozole/L), E2 (500 µg propiconazole/L) and mild to moderate increases in oocyte atresia (1000 µg/L) in the female fish after 21-d exposure. All these effects were produced at similar or higher concentrations than those considered for the environmental classification by the DS (68 µg/L).

The same study also reported effects on egg production at a concentration as low as 5 µg propiconazole/L, but because fecundity in the 50 µg/L treatment did not differ from the controls, the reliability of 5 µg/L as a lowest observable effect concentration for reproductive effects is uncertain. Therefore, RAC notes that this NOEC of 50 µg/L, which is in the same order of magnitude as the value considered by the DS (NOEC of 0.068 mg/L), supports the classification proposed by the DS, namely Aquatic Chronic 1 with an M-factor of 1 based on standard reliable studies.

Two additional studies on aquatic invertebrates were provided regarding synergistic effects of mixtures of products. However, RAC notes that this new information does not change the classification proposed by the DS.

Date	Country	Organisation	Type of Organisation	Comment number
13.05.2016	Belgium		Member State	33
Comment received				
The BE CA supports the proposed M-factors				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for the comment.				

NON-CONFIDENTIAL ATTACHMENTS

1. *Propiconazole Syngenta Public Comments Dev Tox and Skin Sens 2016.zip*. Submitted on 12/05/2016 by Euro Chlor. [Please refer to comments No 16 and 29]