**Committee for Risk Assessment**

**RAC**

Annex 2

**Response to comments document (RCOM)**

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

# Triadimenol (ISO); α-tert-butyl-β-(4-chlorophenoxy)-1*H*-1,2,4-triazole-1-ethanol

**EC Number: 259-537-6**
**CAS Number: 55219-65-3**

CLH-O-0000001412-86-93/F

**Adopted**

**4 December 2015**

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON TRIADIMENOL (ISO); A-TERT-BUTYL-B-(4-CHLOROPHENOXY)-1*H*-1,2,4-TRIAZOLE-1-ETHANOL**

## 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: triadimenol (ISO); α-tert-butyl-β-(4-chlorophenoxy)-1*H*-1,2,4-triazole-1-ethanol**
**CAS number: 55219-65-3**
**EC number: 259-537-6**
**Dossier submitter: United Kingdom**

## GENERAL COMMENTS

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 28.11.2014 | France | | Member State | 1 |
| Comment received | | | | |
| The classification for health hazards proposed by the PRAPeR under DSD was as follow: Xn, R22, Repr. Cat3 R62, R63?, R64<br>Under CLP the proposal for health hazards classification, classification would be:<br>Acute Tox 4; H302<br>Repr Cat 2; H361fd H362<br>So MS FR proposes Acute Tox 4 H302 and Repr Cat 2 H361fd H362 for health hazard classification and MS FR agrees with the classification proposed for Environmental hazards.<br><br>*ECHA note: the following <u>confidential</u> attachment was provided with the comment above (Attachment 1):*<br><br>Format Echa Comments-Triadimenol - Confidential data.doc | | | | |
| Dossier Submitter's Response | | | | |
| We have proposed classification as Acute Tox 4; H302 and Repr Cat 2; H361f. With regards to the MS's proposal for a developmental toxicity classification, please see the response to comment 5. | | | | |
| RAC's response | | | | |
| RAC agrees with the proposed classification as Acute Tox. 4; H302 and Aquatic Chronic 2; H411.<br><br>Regarding reproductive toxicity RAC considers that the developmental toxicity observed in the form of post-implantation losses in rats and rabbits, and the increase in cervical ribs, cleft palates and decreased postnatal viability in rats provide altogether clear evidence of | | | | |

developmental toxicity. The dose-related decrease in pregnancy rates that was observed in all three generations in the multi-generation rat study (with the weak supporting evidence in the form of decreased fertility index in the 2-generation rat study testing only lower doses) and the associated decrease in litter sizes provide clear evidence of reproductive toxicity. RAC considers that the adverse effects on reproduction were not secondary non-specific consequences of parental toxicity, and that there is no evidence that these effects are not relevant to human. In addition, the deficiencies in the multi-generation study do not render the quality of the clear evidence on decreased pregnancy rates in rats less convincing. Although no gross or histopathological examinations of the reproductive organs were performed, adverse effects on sexual function and fertility include e.g. alterations in the female and male reproductive system, adverse effects on gamete production and transport, sexual behaviour, fertility **or** pregnancy outcomes. There is clear evidence of an adverse effect on pregnancy rates and further investigations on the cause of that effect (e.g. gross or histopathological examinations of the reproductive organs) are not required for a specific classification. In addition, pregnancy rates and fertility index were studied only in one species, but studies in the second species are not required in the CLP Regulation in order to conclude on a specific classification for reproduction. As the observed decrease in pregnancy rates could not be assigned to either impairment of sexual function and fertility or to developmental toxicity, RAC considers that Repr 1B; H360 without 'F' and 'D' should be assigned to triadimenol.

In addition, based on the significantly reduced viability index on PND 5 seen in several generations in the multi-generation study together with the information from toxicokinetic studies, it cannot be excluded that triadimenol due to its properties may be transferred to milk. RAC considers that triadimenol should be also classified for effects on or via lactation with H362.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 27.11.2014 | Spain | | MemberState | 2 |
| Comment received | | | | |
| The Spanish CA agrees with the UK proposal for harmonized classification and labelling of triadimenol (in relation to human health) and the CLH report has our approval. | | | | |
| Dossier Submitter's Response | | | | |
| Thank you. | | | | |
| RAC's response | | | | |
| Noted. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 24.11.2014 | Finland | | MemberState | 3 |
| Comment received | | | | |
| The Finnish CA supports the proposed classification Acute tox 4; H302 and Aquatic Chronic 2; H411 for Triadimenol. We also agree with dossier submitters assessment for not to classify according to the following hazard classes: STOT SE, STOT RE, Skin Irrit., Eye Irrit., Skin Sens., Mutagenicity, and Carcinogenicity. | | | | |

| Dossier Submitter's Response |
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| Thank you. |
| RAC's response |
| Noted. |

**TOXICITY TO REPRODUCTION**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 28.11.2014 | Belgium | | MemberState | 4 |
| Comment received | | | | |
| We support the classification for the fertility based on the results provide in the multi-generation study in rats (Loeser & Eiben, 1982) showing a decrease of the pregnancy rate and the viability index at lower dose than the maternal toxicity. Due to the deficiencies in the study (food consumption not measured, fertility of individual males not determined, no histopathological information of the reproductive tissues, no sperm parameter examination, …), the quality of the evidence of the fertility problem is questionable and not sufficient to classify in category 1B. Then a classification in category 2 is required.<br><br>The effects observed on the developmental toxicity (reduced total litter sizes, increased incidences of supernumerary ribs, ..) are observed at a dose at which a maternal toxicity is presented or only in one litter, then we agree with the non-classification for the developmental toxicity. | | | | |
| Dossier Submitter's Response | | | | |
| Thank you. | | | | |
| RAC's response | | | | |
| Noted. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 28.11.2014 | France | | MemberState | 5 |
| Comment received | | | | |
| Development toxicity pp 64-65<br>- In the multigeneration study, pup viability and pup growth were affected with a worsening of the effects through the generations (decrease of 5-d viability index of F3A pups at all tested dose levels). Those effects were not observed in the two generation study (lower tested doses).<br>The classification H362 was agreed at the PRAPeR meeting of Triadimenol taking also into account that in ruminants level in milk decreased rather slowly although significantly lower than in other tissues.<br><br>- Extra ribs: The extra ribs had not been measured in all studies. It is therefore difficult to conclude on their likelihood to persist post-natally. While short supernumerary ribs are transient findings that disappear after birth, full supernumerary ribs seem to be permanent structures. Although they are asymptomatic in rodents, in human cervical ribs are often associated with a pathologic condition known as Thoracic Outlet Syndrome. (Report of the 7th Workshop on the Terminology in Developmental Toxicology Berlin, 4–6 May 2011).<br>Additional cervical ribs are anomalies often observed with triazoles compounds.<br>As for 5 cleft palates, malformation also commonly observed with triazoles, they effectively only occurred in one litter. However, 5 females per group were tested in that range-finding study. Therefore it is questionable to conclude to a genetic link with regard to the small | | | | |

number of dams tested (1 out of 4 litters of the 165 mg/kg/d contained 5/14 foetuses with cleft palates). Although the effects mentioned above were generally associated with maternal toxicity, those effects commonly observed with triazoles compounds are unlikely to be a secondary non-specific consequence of maternal toxicity and classification Repr. Cat2 H361d is warranted.

*ECHA note: the following confidential attachment was provided with the comment above (Attachment 1):*

Format Echa Comments-Triadimenol - Confidential data.doc

Dossier Submitter's Response

We gave careful consideration to whether or not a classification for developmental toxicity should be proposed, taking into account the available evidence and EFSA's opinion, but also recognising that the C&L process undertaken by RAC is separate from EFSA's evaluation.

The decreases in pup survival and body weight gains was associated with maternal toxicity; there was no evidence of a specific effect on development.

In one study in which the supernumerary ribs were measured, they were reported to be small, thus lessening the concern for this finding. The cases of cleft palate occurred in one litter in one rat study; this finding was difficult to interpret because the dose level at which it occurred was higher than those used in the other rat developmental toxicity studies. However, it was not observed in the rabbit studies, in which doses of up to 200 mg/kg/d were administered. Overall, we concluded that there was insufficient evidence to propose a classification for developmental toxicity. We consider that substances should be classified on the basis of the available evidence, not because they belong to a particular class of chemicals.

RAC's response

See response to comments No. 1.

**OTHER HAZARDS AND ENDPOINTS – Physical Hazards**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 28.11.2014 | France | | MemberState | 6 |

Comment received

Section 1.1 impurities: It seems that the technical active substance contains a relevant impurity, it cannot be considered as confidential data so it can be reported in this part.

Section 2.2 - Table 9 Boiling point: It should be clarified if the temperature reported in this part is a boiling point as it seems that it is a temperature of decomposition

*ECHA note: the following confidential attachment was provided with the comment above (Attachment 1):*

Format Echa Comments-Triadimenol - Confidential data.doc

Dossier Submitter's Response

The Buehler assay comprised three induction applications (no information on the impurities in the material tested. Although there were flaws in the GPMT, it provided supportive information and so is not regarded as unacceptable. The available information indicated that

triadimenol was not a skin sensitiser.

With regards to the boiling point, thank you for the observation. Melting was observed in the temperature range of 100 to 160 C, whereas the beginning of exothermic decomposition occurred at 270 C.

With regards to the impurities, full information is provided in the IUCLID and the CLH report can not be updated.

RAC's response

Noted.

**OTHER HAZARDS AND ENDPOINTS – Acute Toxicity**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 28.11.2014 | Belgium | | MemberState | 7 |

Comment received

Based on the LD50 value of 720 (in fasted animals) and 1068 mg/kg (in unfasted animals) obtained in the acute toxicity's study via oral route (Mihail & Thyssen ,1980), we agree with the classification in category 4. However, we consider the dossier as incomplete due to the lack of some information in the studies (no guideline compliant): the deviations or the reliability associated are missing and the mortality at the different dose is not indicated.

Dossier Submitter's Response

For the study by Thyssen & Kimmerle (1980), the following deviations from OECD guideline 401 are noted:

- body weight changes were not reported;
- the reporting of results was limited (clinical signs were reported in summary form only, individual gross necropsy findings were not reported).

The deaths at each dose were:

| Fasted rats | Males | Females |
|---|---|---|
| Dose | Deaths/total number | Deaths/total number |
| 250 | 0/15 | 0/15 |
| 500 | 3/15 | 3/15 |
| 600 | --- | 3/15 |
| 750 | 8/15 | 9/15 |
| 1000 | 13/15 | 13/15 |
| 1500 | 15/15 | 14/15 |
| | | |
| Unfasted rats | | |
| 500 | 0/15 | 1/15 |
| 750 | 1/15 | 0/15 |
| 850 | --- | 4/15 |
| 1000 | 6/15 | 8/15 |
| 1000* | 13/15 | |
| 1250 | | 12/15 |
| 1500 | | 15/15 |

* Mistake in the study report, so it is not clear what the top dose received by males was.

All other available details are included in the CLH report.

| RAC's response |
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| Noted. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 24.11.2014 | Finland | | MemberState | 8 |
| Comment received | | | | |
| In principle we support the suggested classification Acute tox 4; H302 for Triadimenol. If there is no obvious reason why the new guideline study should have preference over the older non guideline study, the lowest LD50 value should be used for classification. However, we think that in this case for transparency, these two critical studies should be reported more accurately in the dossier. | | | | |
| Dossier Submitter's Response | | | | |
| See response to comment 7. | | | | |
| RAC's response | | | | |
| Noted. | | | | |

## OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 27.11.2014 | Germany | | MemberState | 9 |
| Comment received | | | | |
| The German CA acknowledges the additional amount of work caused by the two studies by Teigeler (2007) and Bomke (2010) on endocrine-mediated effects of Triadimenol. As they were made available only after the Public Consultation of a previously, in 2011 started CLH-procedure, the initial CLH dossier was withdrawn for revision.<br>We appreciate that the studies and the German evaluation have been included in the UK CLH dossier. In general we agree that in a CLH dossier different interpretations of the same dataset can/should be presented for RAC or other interested stakeholders.<br>However, in the actual CLH dossier we would prefer a more objective and clear presentation of the arguments without specifying certain national authorities.<br>We therefore would appreciate if RAC could formalize the presentation of the different argumentations without naming and directly quoting "UBA".<br><br>Concerning the principal question whether endocrine-mediated effects should be considered for the purpose of classification and labelling (C&L) we would like to point out that according to GHS and CLP C&L is hazard based and relates to the intrinsic properties of a substance. Therefore the use of additional chronic data for fish to evaluate the intrinsic properties of Triadimenol to harm the aquatic environment, like the new two studies on endocrine-mediated effects, is necessary and in accordance with the principles for C&L.<br><br>Therefore the German CA proposes for Triadimenol a classification as Aquatic Chronic 1 (H410) with a M-Factor of 1, because the lowest valid NOEC is in the range of 0.01 < NOEC ≤ 0.1 mg/L for not rapidly degradable substances.<br><br>*ECHA note: The following <u>confidential</u> attachment was provided with the comment above (Attachment 2):*<br><br>Triadimenol_Bomke_Study_2010_Graphic.docx | | | | |

| Dossier Submitter's Response |
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| We note DE's views on the two newly considered fish ED studies - and we respond regarding these, as well as the general principal of using their endpoints for classification, in relation to DE's more detailed comments (No. 11) further below... |
| RAC's response |
| Noted, RAC considered the argumentation by DE and the option to classify as aquatic chronic 1, H410 with an M-factor of 1.<br>RAC does consider the endpoint sex ratio as a reprotoxic and adverse effect on population level and consequently as relevant in relation to aquatic hazard classification. According to OECD TG 234, the endpoint sex ratio is to be determined via gonad histology. Optionally, evaluation and staging of oocytes and spermatogenetic cells may also be determined.<br>RAC understands that the Fish Sexual Development Test (FSDT) (Bomke, 2010) was carried out parallel to the development of the OECD TG 234 for the Fish Sexual Development Test and does not fulfil fully the current version of the guideline. It was evaluated reliable only with restrictions and several experimental draw backs have been discovered by the data owner. RAC notes that the tested species fathead minnow (*Pimephales promelas)* is no longer included in OECD TG 234. It is also considered to be less sensitive to the core endocrine endpoints aromatase inhibition and sex differentiation (Koenig & Bomke, 2010). The data owner confirmed that all fish were either males or females based on gonad histology and no undifferentiated or intersex fish were seen. In contrast, the re-evaluation of the sex ratio submitted by DE used a discrepancy between phenotypic sex and histological sex to determine undifferentiated or intersex fish and to derive a NOEC of 70.8 µg/L.<br>RAC considers this procedure and the NOEC not appropriate for the purpose of aquatic hazard classification. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 28.11.2014 | Belgium | | MemberState | 10 |
| Comment received | | | | |
| Based on the results of the aquatic acute toxicity tests (all LC50 for the 3 trophic levels >1mg/l) we agree that the substance needs no classification for acute toxicity.<br><br>For aquatic chronic toxicity however we are of the opinion that the results of the reliable 21d fish screening assay( OECD230) should be taken into account when classifying the substance.<br>- Annex I, 4.1.2.7.2 of CLP states that "for determining chronic aquatic toxicity for classification purposes data generated according to the standardised test methods referred to in Article 8(3) shall be accepted, as well as results obtained from other validated and internationally accepted test methods. The NOECs or other equivalent ECx (e.g. EC10) shall be used."<br>- In chronic studies, lethal and sub-lethal effects are assessed in order to determine the no observed effect concentration (NOEC). In the liver, changes, including single cell necrosis, condensed hepatocellular cytoplasm and a slight increase of fatty vacuolation, were observed at 300 µg a.s./L. Even if they are considered as minimal or slight effects, we cannot neglect this liver toxicity which is not an ED endpoint. A NOEC of 0.03mg/l should be considered for classification purposes and fish becomes the most sensitive species instead of invertebrates (Daphnia with NOEC mortality = 0.145mg/l instead of Pimephales promelas with NOECgrowth=0.17mg/l).<br>Adding thereto the fact that the substance is considered as not rapidly degradable, we find it more appropriate to classify it as aquatic chronic 1, H410. An M-factor of 1 (0.01mg/l< | | | | |

NOEC≤0.1mg/l) should than be used.

Some editorial or/and minor comments:
* 5.4.2.2 long term toxicity to aquatic invertebrates
P83-84 : in table 25 a 21dNOECreproduction for Daphnia magna of 1.25mg/l is given for the OECD211-test performed with a purity of 97.3%, while in the explicatory part of this test a 21dNOECreproduction of 1.28mg/l is given.

Dossier Submitter's Response

We note BE's agreement regarding the proposal for no acute aquatic classification.
With regards to the chronic classification, BE's comments on the newly assessed fish ED studies are similar to those presented by DE above and below - so please refer to our response to DE's comments on this (No. 11 below).

We thank BE for their editorial correction - the reference to a 21d $NOEC_{reproduction}$ for *Daphnia magna* of 1.25 mg a.s./L in Table 25 is incorrect and it should indeed be 1.28 mg a.s./L as reported in the subsequent detailed text and Conclusion (Section 5.6).

RAC's response

Noted, RAC considered the argumentation by BE and the option to classify as aquatic chronic 1, H410 with an M-factor of 1. However, RAC without any further guidance and clarification considers such effects not relevant in relation to aquatic hazard classification.
This argumentation is in line with the recent RAC assessment of tebuconazole where a Fish Sexual Development Test (FSDT) with fathead minnow gave information on effects (degenerative liver toxicity, reduction in yolk accumulation and pancreas effects) at levels lower than those effects 'traditionally' used for chronic classification (e.g. growth, survival, reproduction). RAC, along with the Evaluating MSCA and DS, agreed in the case of tebuconazole that whilst such studies might provide supporting data when based on endpoints for mortality, growth and fertility, such effects (some of which may be ED-related endpoints) were currently not considered as a sole basis for the purposes of aquatic hazard classification.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 27.11.2014 | Germany | | MemberState | 11 |

Comment received

p.74 point 5.4.1.2 Long term toxicity to fish
Table 24: The German CA propose to add to the test results from Bomke C. (2010) the NOEC= 0.0708 mg a.s./L (nominal) related to the chronic endpoint sex ratio of fish.

p.76 Fathead minnow, fish screening assay- Triadimenol (Teigeler, M. 2007)
The study is evaluated as valid and reliable without restriction (Klimisch 1). The NOEC was examined as 0.030 mg/L a.s. There is no reason for refusing these results for C&L purposes.

p.79 Triadimenol- FSDT report with fathead minnow (Bomke, C. 2010)
The study is evaluated as valid and reliable only with restrictions related to not sufficient data for vitellogenin. The following citation is from the first evaluation of the FSDT report (Bomke, 2010) by the German Federal Environment Agency (UBA) in 2011, delivered to the UK CA in 2013:
"VTG concentration, nuptial tubercle and histology of the male genitals are the most sensitive endpoints in the test system. The statement of the author of the test report that no significant effects occurred (NOEC >= 170 µg/L) cannot be agreed with, in particular due

to the sex ratio (ratio of distinct females) and the VTG plasma concentration of the males (median). Therefore, a preliminary NOEC of 70.8 µg/L based on sex ratio is derived."
It is clear that the NOEC of this study is at the moment of first evaluation 0.0708 mg/L. Perhaps it would be lower if later more precise vitellogenin data are available.
Therefore we do not support the proposal of the UK CA that the complete study is not entirely reliable and currently a NOEC cannot be determined from this study.

p.85/86 conclusion on classification and labelling
The newly available data give the clear evidence that the chronic aquatic toxicity to fish of Triadimenol is below NOEC = 0.17 mg/L (Nieden and Lam 2007).
The long-term data for fish NOEC = 0.03 mg/L from a valid and reliable FSA study (Teigeler, 2007), in contribution to a NOEC = 0.0708 mg/L (nominal) from a valid and reliable FSDT study (Bomke, 2010), are the lowest long term data for aquatic organisms for Triadimenol.
Triadimenol should therefore be classified as Aquatic chronic 1 (H410) with a M-Factor of 1, because the lowest valid NOEC is in the range of 0.01 < NOEC ≤ 0.1 mg/L for not rapidly degradable substances.

*ECHA note: The following <u>confidential</u> attachment was provided with the comment above (Attachment 2):*

Triadimenol_Bomke_Study_2010_Graphic.docx

Dossier Submitter's Response

We note DE's views on the fathead minnow Fish Screening Assay (FSA) (Teigeler, 2007) and Fish Sexual Development Test (FSDT) (Bomke, 2010). We address the points raised in turn, along with the general principal question regarding whether endocrine-mediated and/or liver histopathology effects should be considered for classification and labelling purposes (comment 9). Our response on the FSA also addresses this principal and BE's point made above (comment 10):

Re: p.74, Table 24. The UK CA still does not agree that a clear and reliable NOEC for classification purposes is obtainable from FSDT by Bomke (2010). This is discussed further below.

Re: p.76-79 and final Conclusion (p.85/86, Section 5.6). We agree that the FSA by Teigeler (2007) is a valid study - although not entirely clear in all its effects. We also agree that an overall NOEC of 0.03 mg a.s./L can be determined. This is based on the following results seen at a LOEC of 0.3 mg a.s./L:

- A statistically significant reduction (of around 38% compared with control) in vitellogenin (VTG) levels in female fish.
- Histopathological changes in the liver described as 'slight'. These comprised condensed hepatocellular cytoplasm (lower grade 2/3 effects) in 3 out of 8 male fish (no concentration-related increase in females); single cell necrosis (grade 1) in 1 female out of 16; fatty vacuolation (grade 1-2) in 2 out of 8 males and 2 out of 16 females.

It was proposed by the authors and data holder that the effects at 0.3 mg a.s./L might represent a 'borderline' level for liver toxicity and that these 'incipient' liver changes *may* be linked (through subsequent aromatase inhibition) to the reduction in female VTG levels.

Of all the other histopathological (inc. gonads), sexual (male VTG, nuptial tubercles and secondary sexual characteristics), morphological and growth (inc. weight, length) and more 'apical' fertility (fertilisation rate and fecundity) parameters investigated, none were statistically significantly affected or clearly concentration-related.

DE and BE have proposed that there is no reason for *not* using the results for female VTG reduction and/or the possibly connected slight liver changes (and thus the NOEC of 0.03 mg/L) for classification purposes.

In the CLH Report, it was proposed that irrespective of whether the FSA NOEC is based on potential ED effects (i.e. female VTG) or on slight histopathological liver changes, such effects are not normally considered relevant in relation to aquatic hazard classification. Whilst the CLP legislation and guidance does suggest that the lowest reliable NOEC is employed, it does not specifically address which effects should be used as the basis for NOEC derivation and chronic classification. So far (including under the Dangerous Substances Directive) the chronic environmental classification has generally been based on effects such as reductions in growth, survival or more apical reproductive parameters which could more clearly be anticipated to lead to 'harm' at a population level - rather than on changes in hormones, gene expressed proteins, biomarkers or slight histopathology in single organs. The previous RAC assessment of tebuconazole was cited where potential ED-related effects and histopathological liver changes were discussed but were not used as a sole basis for classification. The German DAR for spiroxamine (currently being considered for classification by the RAC) also states that 'non-classical biomarker end points' (e.g. histopathology and blood VTG) are not used as population-relevant parameters from a FFLC study. Therefore there is an issue of consistency here.

However, the UK CA did propose in the triadimenol CLH Report that it would be helpful to 'flag up' the use of such endpoints for further public, MS and RAC consultation with the aim of updating CLP guidance on this matter. Whilst we would retain the proposed Chronic Category 2 classification for triadimenol, we do agree that the comments from DE and BE regarding the use of ED and histopathology-related endpoints for environmental classification would benefit from further guidance development.

Regarding DE's proposal to use their suggested NOEC of 0.0708 mg a.s./L from the FSDT with fathead minnow (Bomke, 2010, p.79-83) in the Conclusion on chronic classification (p.85/86, Section 5.6). Having considered the methodology and reporting of effects in the FSDT study, as well as DE's and the data holder's assessment of it, the UK CA came to the conclusion that its results could not be relied upon for classification purposes.

DE have highlighted that, in particular due to an apparent difference in sex ratio from controls (ratio of distinct females) and median VTG plasma concentration in males, a preliminary NOEC of 0.0708 mg/L could be derived (instead of ≥0.17 mg/L (highest concentration tested) for these parameters proposed by the study author and data holder). These two aspects are discussed further below:

- It is not clear if DE's re-evaluation of the sex ratio is based on secondary sexual/morphological characteristics but this indicates a statistically significant ($p = 0.05$) reduction in females at a LOEC of 0.17 mg/L and thus a NOEC of 0.0708 mg/L (nominal). The data holder argues that the FSDT Guideline (OECD 234) states that sex (male, female, intersex and undifferentiated) should be determined based on histological examination of the gonads (with further guidance on this given in OECD GD 123). When this is done, they consider the sex of all individuals could be clearly identified based on histological determination and no significant difference was observed, thus the NOEC of 0.17 mg/L from the original report was considered valid.
- With regards to VTG plasma concentrations in males, DE suggest that although an apparent concentration-response effect does not persist up to the highest test concentration, this could be due to a regulation at the highest level which compensates any endocrine mechanism. The data holder argues that this is speculation and also that

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| an alternative suggestion that toxic effects are predominating at the higher concentration, preventing a further sex shift, is not in line with the histopathological results in the liver. Whilst the mean VTG concentration in males was significantly increased compared to the control at 0.0708 mg/L, the measured VTG concentrations at the highest level were in the same range as the control. Therefore, a suggested NOEC of 0.17 mg/L was given in line with the original study report.<br><br>The UK CA noted in the CLH Report that there were other aspects of how the FSDT was performed (including lost and redistributed fish which could have influenced sexual development and low control hatching success and survival) and these called in to question clear interpretations and certainty over cause and effect in the study. Rather than debate further over what *can* be clearly interpreted from this study, and in the absence of a reliable repeat study, the UK CA suggests that the results from this FSDT be disregarded for hazard classification. This is separate to the question of principal over whether the possible effects observed should, in any case, be used for classification (see above). |
| RAC's response |
| Noted, RAC considered the argumentation by DE and the option to classify as aquatic chronic 1, H410 with an M-factor of 1. Please refer to response by RAC to comments No. 09 and 10. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 24.11.2014 | Finland | | MemberState | 12 |
| Comment received | | | | |
| The Finnish CA supports the proposed classification Aquatic Chronic 2; H411 for Triadimenol. | | | | |
| Dossier Submitter's Response | | | | |
| We acknowledge the Finnish CA's support regarding the proposed environmental classification. | | | | |
| RAC's response | | | | |
| Noted | | | | |

## CONFIDENTIAL ATTACHMENTS RECEIVED

1. Classification and labelling of dangerous substances - French comments on Triadimenol (55219-65-3). Filename: Format Echa Comments-Triadimenol - Confidential data.doc. Submitted by France on 28.11.2014. [*Please refer to comments 1, 5 and 6*]

2. Filename: Triadimenol_Bomke_Study_2010_Graphic.docx. Submitted by Germany on 27.11.2014. [*Please refer to comments 9 and 11*]