COMPILED COMMENTS ON CLH CONSULTATION

Comments provided during consultation are made available in the table below as submitted through the web form. Please note that the comments displayed below may have been accompanied by attachments which are listed in this table and included in a zip file if non-confidential. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Last data extracted on 02.02.2024

Substance name: tebuconazole (ISO); 1-(4- chlorophenyl)-4,4-dimethyl-3- (1,2,4-triazol-1-ylmethyl)pentan-3-ol
CAS number: 107534-96-3
EC number: 403-640-2
Dossier submitter: Denmark

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
17.01.2024	France	Task Force (Adama, Albaugh, Bayer, Nufarm)	Company-Manufacturer	1
Comment received				
Tebuconazole Task Force is of the opinion that a revision is needed to take all the scientific information into consideration in a well-balanced weight of evidence. There appears to be a disproportionate emphasis on publications (regardless of their reliability) over standard studies (GLP and OECD), notably evident in the comments concerning toxicity on reproduction and development. Comments are also available on the ED assessment and are provided as attached document in the field « Confidential attachment ». ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tebuconazole_Commenting table_CLH_report_20240116_sanitised.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Tebuconazole_Commenting_tables.zip				

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2024	Netherlands		MemberState	2
Comment received				
It would be helpful to have more information in some of the tables such as table 30 and table 31, page 28-32, on the studies performed, for instance, the exposure duration and use of positive and negative controls. In table 35, page 38-39 important experimental conditions are missing including the species. In our view such information should be presented in the report, not just Vol 3. In Table 47, page 52, the exposure concentrations used for the study are missing as described in Vol 3 B 6.6.3/07. In table 33, page 37, it is referred to tables 53-55 for more information on the effect size of				

histopathology and clinical chemistry/heamatology of reference Vol 3 B.6.5.2/02. Please check this, because it seems to refer to other information.

According to page 56, study B6.6.3/07 showed a seven-fold increase in late-gestation progesterone levels, which is not included in Table 47.

HEALTH HAZARDS – Acute toxicity

Date	Country	Organisation	Type of Organisation	Comment number
10.01.2024	Germany		MemberState	3
Comment received				
Based on the LD50 of 1700 mg/kg bw, the classification into Cat. 4 (H302) is supported.				

Date	Country	Organisation	Type of Organisation	Comment number
17.01.2024	France	Task Force (Adama, Albaugh, Bayer, Nufarm)	Company-Manufacturer	4
Comment received				
We agree with the proposed classification for acute oral toxicity (page 17). We agree with the proposal that no classification is required for acute dermal toxicity (page 18) and acute inhalation toxicity (page 20). ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tebuconazole_Commenting table_CLH_report_20240116_sanitised.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Tebuconazole_Commenting_tables.zip				

HEALTH HAZARDS – Skin corrosion/irritation

Date	Country	Organisation	Type of Organisation	Comment number
17.01.2024	France	Task Force (Adama, Albaugh, Bayer, Nufarm)	Company-Manufacturer	5
Comment received				
We agree with the proposal that no classification is required for skin irritation (page 22). ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tebuconazole_Commenting table_CLH_report_20240116_sanitised.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Tebuconazole_Commenting_tables.zip				

HEALTH HAZARDS – Serious eye damage/eye irritation

Date	Country	Organisation	Type of Organisation	Comment number
17.01.2024	France	Task Force (Adama, Albaugh, Bayer, Nufarm)	Company-Manufacturer	6
Comment received				
We agree with the proposal that no classification is required for eye irritation (page 25).				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tebuconazole_Commenting table_CLH_report_20240116_sanitised.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Tebuconazole_Commenting_tables.zip

HEALTH HAZARDS – Respiratory sensitisation

Date	Country	Organisation	Type of Organisation	Comment number
17.01.2024	France	Task Force (Adama, Albaugh, Bayer, Nufarm)	Company-Manufacturer	7
Comment received				
We agree with the proposal “not applicable” for respiratory sensitisation (page 26). ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tebuconazole_Commenting table_CLH_report_20240116_sanitised.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Tebuconazole_Commenting_tables.zip				

HEALTH HAZARDS – Skin sensitisation

Date	Country	Organisation	Type of Organisation	Comment number
17.01.2024	France	Task Force (Adama, Albaugh, Bayer, Nufarm)	Company-Manufacturer	8
Comment received				
We agree with the proposal that no classification is required for skin sensitisation (page 28). ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tebuconazole_Commenting table_CLH_report_20240116_sanitised.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Tebuconazole_Commenting_tables.zip				

HEALTH HAZARDS – Germ cell mutagenicity

Date	Country	Organisation	Type of Organisation	Comment number
17.01.2024	France	Task Force (Adama, Albaugh, Bayer, Nufarm)	Company-Manufacturer	9
Comment received				
We agree with the proposal that no classification is required for germ cell mutagenicity (page 34). ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tebuconazole_Commenting table_CLH_report_20240116_sanitised.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Tebuconazole_Commenting_tables.zip				

HEALTH HAZARDS – Carcinogenicity

Date	Country	Organisation	Type of Organisation	Comment number
17.01.2024	France	Task Force (Adama,	Company-Manufacturer	10

		Albaugh, Bayer, Nufarm)		
Comment received				
We agree with the proposal that no classification is required for carcinogenicity (page 51). ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tebuconazole_Commenting table_CLH_report_20240116_sanitised.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Tebuconazole_Commenting_tables.zip				

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2024	Netherlands		MemberState	11
Comment received				
On page 49, table 46, a compilation of factors is to be taken into consideration in the hazard assessment. The data from the first mouse study with the reported hepatocellular tumours as seen in table 38 is missing. The NL-CA suggests to clarify the assessment of the relevance of liver tumors as observed in the second study in mice. The conclusion at page 50 suggests that the tumors are considered not relevant based on the mode of action (via CAR/PXR receptor). However, the conclusion at page 53 indicates that tumors are not considered relevant for humans based on the mode of action as well as the high dose exceeding the MTD. Regarding the assessment of exceedance of the MTD, it is also suggested to provide further information on systemic toxicity observed in the second mouse study. The report describes the effects observed in the liver, but not any systemic effects including changes in body weight and clinical signs. To determine if the MTD was exceeded, such information is needed. In addition, the liver toxicity seems to be transient and more profound during the interim phase as compared to the terminal phase. Also, please discuss the liver toxicity in light of the liver tumors. The carcinogenic effects may be preceded by the liver toxicity or co-exist with it. In this light the liver tumors may be relevant. Further information on the systemic toxicity is needed to determine if the MTD is indeed exceeded and if the liver tumors could be relevant. On page 50 comparison with the CLP criteria it is stated by the RMS that "…hepatocyte proliferation does not occur in human hepatocyte cultures exposed to tebuconazole, which clearly confirms that human hepatocytes are not sensitive to a key event in this MoA.". The Netherlands politely disagrees with this conclusion and asks the DS to include and reflect on the ongoing discussion regarding the human relevance of the mode of action (MoA) for liver tumor formation by chemicals that are activators of the constitutive androstane receptor (CAR). In 2021 a comprehensive review article by Yamada et al. was published which concluded that the MoA is not plausible for humans based on a lack of replicative DNA syntheses (RDS) in in vitro studies using cultured human hepatocytes and in vivo studies with chimeric mice bearing human hepatocytes and additionally epidemiological data on the known CAR-activator phenobarbital and limited data on other CAR-activators. In response to this review, scientists from the National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands sent a letter to the editor questioning the robustness of the systems used for investigating the proliferative effects and also stating that the evidence to support the claim is too small. Currently, there is no ECHA guidance on this MoA available, and therefore, the Netherlands is of the opinion the CAR MoA should not yet be used to support a non-human relevance claim. Hence, these tumors should not be dismissed based on the CAR MoA. It is too premature to conclude that the species difference is evident for CAR-mediated liver tumor formation.				

Overall, the NL-CA is of the opinion the tumor effects may be relevant as it is not very clear if the MTD is exceeded and the CAR MoA should not be used to support non-human relevance claims at this time.

HEALTH HAZARDS – Reproductive toxicity

Date	Country	Organisation	Type of Organisation	Comment number
18.01.2024	Germany	<confidential>	Company-Manufacturer	12

Comment received

It is proposed by the DK-RMS to classify Tebuconazole Repr. 1B, H360F – May damage fertility.
The main adverse fertility effects mentioned are:
1) dystocia and prolonged gestation, and
2) effects on the reproductive system of perinatally exposed males

Regarding 1):
The results of the developmental neurotoxicity study (B.6.6.2.1.2/01) suggest that the duration of gestation was prolonged (statistically significant, by half a day) but is within the historical control data (as depicted in M-581075-04-1_MCA05 submitted under PPPR). Moreover, this effect has not been observed in the two-generation study (B.6.6.1.1/01) with a longer period of exposure.
B.6.6.3/07 is considered not reliable based on small number of animals, inconsistent findings with other publications from the same group (e.g. B.6.6.3/04), reporting deficiencies. Therefore, results reported in this study with respect to dystocia and prolonged gestation are unreliable and shall not be used to derive a classification for fertility.
The comments' submitter considers the publication B.6.6.3/04 of limited relevance as mixtures were evaluated as well as unreliable based on small number of animals, inconsistent findings with other publications of the same study from the same group and reporting deficiencies.
The prolonged gestation as assessed by DK-RMS is not considered relevant for classification for fertility effects since there is no clear effect as also stated during PRAPeR (June 2008): "The experts discussed the effects observed in the study and in particular the increased gestation lengths at the highest dose. According to the experts these were not clear effects. Also, in the multigeneration study such an effect was not seen. Overall, the experts agreed that a classification for fertility should not be proposed."
Regarding the mode of action analysis the comments' submitter wants to point out that, based on the ED assessment performed under PPPR by the applicant Bayer AG, an alternative MoA involving CAR/PXR activation is supported (M-684128-01-1).

Regarding 2):
Additional studies available from the public literature which were also used by DK-RMS to assess potential effects of tebuconazole on fertility (e.g. Taxvig et al., 2007 or Hass et al., 2008/2012). However, those studies are considered unreliable based on small number of animals, inconsistent findings with other publications from the same group, and reporting deficiencies.
Regarding the mode of action analysis the comments' submitter wants to point out that, based on the ED assessment performed under PPPR by the applicant Bayer AG, an alternative MoA involving CAR/PXR activation is supported (M-684128-01-1).

Commenting discussion and conclusion of B.6.6.1.1/01 by DK-RMS
(Two-generation dietary study in rats)
The number of stillborn pups did not differ significantly from control values, did not show

dose correlation, was in accordance with historical control data (18 studies conducted at Bayer from 1981-1986: 0-16, same rat strain, same breeder), and nearly all females with any stillbirths delivered dead pups only in one of the two litters. In the control group and in the 1000 ppm group only one F0 and F1B female each delivered dead pups in both litters. This observation is considered to be within the normal variation expected for this endpoint in this rodent strain.
Moreover, in both matings of the F0 generation, viability and/or lactation indices were slightly reduced compared to the current control at 1000 ppm (lactation indices within historical control data). No dose-related effect was observed at 100 and 300 ppm. In both matings of the F1B generation, neither viability nor lactation indices were altered. Since the F1 generation was much longer exposed to the compound the reduction in the F0 generation is most likely due to biological variability.
The litter size was reduced at 1000 ppm in the F0 generation but not in the F1B generation. In contrast, a slightly increased litter size occurred at 1000 ppm at the 2nd mating of the F1B. Since the F1 generation was much longer exposed to the compound but did not show effects on litter size the reduction in the F0 generation was most likely due to normal biological variation.
Furthermore, parental toxicity was observed at the highest dose tested by the dietary route of 1000 ppm (72/97 mg/kg bw/day F0/F1 males, 94/111 mg/kg bw/day F0/F1 females); body weight gain and food consumption were reduced during the pre-mating, gestation and lactation periods.
The comments' submitter considers the effects on pup body weights secondary to maternal effects.

It is proposed by the DK-RMS to classify Tebuconazole Repr. 1B, H360D - May damage the unborn child.
The main adverse developmental effects are:
1) post implantation loss and perinatal death,
2) foetal/pup growth impairment, and
3) external malformations including cleft palates

Commenting discussion and conclusion of B.6.6.2.1.1/01 by DK-RMS
(Developmental toxicity in rats after oral exposure)
Malformations (micro-/anophthalmia, multiple malformations including dysplasia of long bones) are known as common malformations in the strain of rats used. The predominant malformation observed at 100 mg/kg bw/d was micro-/anophthalmia which is the most frequent spontaneous malformation in this rat strain from this specific breeder. Thus, due to the different and common types of malformations observed at 100 mg/kg bw/d and the absence of treatment-related eye malformations in studies using animals from a different breeder (please refer to B.6.6.2.1.1/02) a specific effect of tebuconazole is not indicated.

Commenting discussion and conclusion of B.6.6.2.1.1/02 by DK-RMS
(Developmental toxicity in rats after oral exposure)
It is true for this study that in the high dose group the reduced litter weight fully explains the reduced maternal bw gain during pregnancy. Nevertheless, in B.6.6.2.1.1/03 also corrected reduced body weight of dams was shown at a dose of 120 mg/kg bw/d.

Commenting discussion and conclusion of B.6.6.2.1.2/01 by DK-RMS
(Developmental neurotoxicity in rats)
The comments' submitter considers the rationale for fertility effects not sufficient. One dam died GD 23 with dystocia but with severe kidney and urinary bladder findings.
The UK RMS conclusion, to which DK RMS agrees, states that the dose of 1000 ppm is excessively toxic for F1 generation. Effects at doses where excessive toxicity is observed are

not considered relevant for identification of ED effects. The comments' submitter considers the delay of vaginal patency as a secondary effect based on the retarded growth (12% lower body weight than control).
The comments' submitter does not agree with the identification of a neurodevelopmental effect. Brain weight and cerebellar thickness were reduced (on PD 12) whilst the ratio of brain weight to terminal body weight was significantly greater than control but no effect on other measurements or histopathology was observed.

Commenting discussion and conclusion of B.6.6.2.2.1/04 by DK-RMS
(Developmental toxicity in rabbits after oral exposure)
The statement that "no further foetal examinations were performed" is not correct. Foetuses were evaluated externally but no external findings were observed.
Moreover, rabbits are known to be very sensitive to glucocorticoids regarding malformations. Therefore, in the comments' submitter's opinion, it is concluded that, besides distinct maternal toxicity, also only slight adrenal hypertrophy might have contributed to the malformations seen in rabbits at 100 mg/kg bw/d. Hormone levels were not addressed in this study.

Commenting discussion and conclusion of B.6.6.2.3.1/01 by DK-RMS
(Developmental toxicity in mice after oral exposure)
DK-RMS proposes a LOAEL of 30 mg/kg bw/d based on an increased number of runts at that dose. The comments' submitter does not agree since the increased number of runts was not supported by a significant decrease in foetal weight (neither at 30 nor 100 mg/kg bw/d: -4% at 100 mg/kg bw/d) and is thus disregarded. Therefore, a NOAEL of 30 mg/kg bw/day is derived.
Moreover, DK-RMS evaluates the increased number of malformations as adverse effects observed in the high dose group. An increased incidence of malformation - 13 foetuses in 8 litters cf. single incidence in controls was observed. Nevertheless, malformation were primarily cleft palate, a common observation in mice.

Commenting discussion and conclusion of B.6.6.2.3.1/03 by DK-RMS
(Developmental toxicity in mice after oral exposure)
The comments' submitter does not agree on a maternal NOAEL of 100 mg/kg bw/d but considers this dose level the maternal LOAEL based on: ↓ body weight gain days 6-16 (-13%), ↓ food consumption days 6-16 (-4%), ↑ relative liver weight (20%), ↑ lipid storage, clinical chemistry and histopathology, ↑ reticulocytes, ↑ spleen weight (45%)
Furthermore, the comments' submitter does not agree on a fetal LOAEL of 10 mg/kg bw/d since the non-significant ↑ post-implantation loss (12.5% cf. 8.4% controls) with no ↓ number live fetuses is considered an incidental finding. Therefore, the LOAEL should be set at 100 mg/kg bw/d.

Commenting discussion and conclusion of B.6.6.2.3.2/01 by DK-RMS
(Developmental toxicity in mice after dermal exposure)
The comments' submitter does not agree to the developmental NOAEL of 300 mg/kg bw/d since the observed malformations are not clearly treatment-related but spontaneous in origin. NOAEL should therefore be set at 1000 mg/kg bw/d.

In general, the comments' submitter does not agree on the human health assessment of the DK-RMS included in the CLH report with regard to the topics listed below.
Since those topics are interlinked as they partly refer to the same endpoints and studies, the comments' submitter prepared a separate document in the active substance renewal process of tebuconazole under BPR to provide a better overview than could be reached by only commenting single endpoints. The document "Response from applicant regarding main human hazard discussions on tebuconazole assessment performed by eCA (dRAR and

IUCLID)" was provided to the eCA DK separately and directly based on data ownership. The following topics are addressed which are based on a rationale also submitted under PPPR (by Bayer AG):
• Classification with Repr. 1B, H360FD including
• mouse as a (non)suitable species for derivation of classification
• historical control data for developmental toxicity study in the rabbit and related NOAEL derivation
• Identification of tebuconazole as an "endocrine disruptor for human health"
Redacting this document would make its reason obsolete. Therefore, it was not submitted as confidential document since the instructions on the commenting site state that "If you submit a confidential attachment, please also provide a version with confidential parts removed/blanked out, which will be published on ECHA's website". Nevertheless, the comments' submitter wants DK-RMS to notify of this document and request to take the represented rationale as well into account.

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2024	France	Générations Futures	National NGO	13

Comment received

Generations Futures agrees with the assessment performed by the DK-RMS and is of opinion that tebuconazole should be classified as reprotoxic, category 1Bfd.

Regarding sexual function and fertility, The main adverse effects observed are 1) dystocia and prolonged gestation and 2) effects on the reproductive system of pubertally exposed males. These effects have been observed for doses responsible of body weight gain in early pregnancy and reduced food consumption which are not considered as marked systemic toxicity. The adverse effects observed on fertility are therefore not secondary consequences of systemic toxicity. Thus, they are sufficient for a classification in category 1B according to the CLP criteria.
Regarding effects on development, as highlighted by the RMS, there are clear evidence of adverse effects that are not considered to be secondary non-specific effects of other toxic effects. Criteria for classification in category 1B are therefore also met for development.

Generations Futures would like to point out that the classification of tebuconazole as a category 1B reprotoxicant was already being considered by EFSA experts since 2014 as indicated in the peer review: "Some experts noted that, based on the severity of effects already seen at low dose in the mouse pups, without maternal toxicity, a classification Repr. 1B H360D "May damage the unborn child" might even be considered." https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2014.3485 (EFSA peer review of 2014: EFSA (European Food Safety Authority), 2014. Conclusion on the peer review of the pesticide risk assessment of the active substance tebuconazole. EFSA Journal 2014;12(1):3485, 98 pp. doi:10.2903/j.efsa.2014.3485)

We also highlighted that tebuconazole is considered as a reprotoxic and an endocrine disruptor since 2012 by the Danish centre on endocrine disrupters who concluded the following:
No relevant human data was found. Studies show that tebuconazole has an anti-estrogenic and anti-androgenic mode of action in vitro. Tebuconazole induced adverse effects on reproductive development in the offspring after exposure in utero, i.e. virilised the female offspring, and caused feminizing effects in male offspring. Moreover, tebuconazole increased gestational length and increased progesterone levels. Tebuconazole cause vitellogenin induction in fish. Evaluation: Endocrine disrupter in category 1.
(ref: https://mst.dk/media/mst/9106715/chemicalsreportandannex.pdf) (Assessment of

the Danish centre on endocrine disruptors, 2012 (not 2014 as mentioned in the comment): Hass, U., Christiansen, S., Petersen, M. A., Boberg, J., Andersson, A-M., Skakkebæk, N. E., Bay, K., Holbech, H., Lund Kinnberg, K., & Bjerregaard, P. (2012). Evaluation of tebuconazole, triclosan, methylparaben and ethylparaben according to the Danish proposal for criteria for endocrine disrupters. Danish Centre on Endocrine Disrupters).

The French National Institute for the Industrial Environment and Risks (INERIS) also considers the tebuconazole as an endocrine disruptor since 2021. They concluded (in French) : « En prenant en compte l'ensemble de ces résultats, et les indications fournies par le guide européen d'identification des EDCs (ECHA/EFSA, 2018), on peut considérer que le tébuconazole remplit les critères d'identification de perturbateur endocrinien chez les mammifères
(ref: https://hal.science/ineris-03225131/ /
https://professionnels.ofb.fr/sites/default/files/pdf/documentation/Pollution/PerturbateursEndocriniens/PE%20dans%20les%20NQE%20-%20Phase%20II%20-%20etude%20de%20cas%20tebuconazole.pdf) (Assessment of INERIS, 2021: Vers une meilleure prise en compte de la perturbation endocrine dans les normes de qualité environnementale – Phase II : application du guide européen d'identification des perturbateurs endocriniens pour les pesticides & biocides et implications pour l'établissement des valeurs seuils. Une étude de cas : le tébuconazole - Ineris - 181216 - 1994313 - v4.0 – 11/02/2021)

Based on these clear evidence regarding the reprotoxicity and the endocrine disruption properties of tebuconazole, available for 10 years, Générations Futures has launched a legal actions against the fifth prolongation of the authorisation of tebuconazole in September 2023. (see our report: https://www.generations-futures.fr/wp-content/uploads/2023/12/recours-6-sa-ue_vf.pdf) (Report of Générations Futures : Générations Futures conteste la prolongation de l'approbation européenne de 5 pesticides. Générations Futures, 11/12/2023)

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2024	Netherlands		MemberState	14
Comment received				
The NL-CA agrees with the proposed Repr 1B classification for reproductive toxicity (i.e. adverse effects on fertility and sexual function and adverse effect on development). In the CLH report references are made to the endocrine disrupting activity of tebuconazole, but it is unclear if tebuconazole is considered to be endocrine disrupting in light of the current criteria for endocrine disruption.				

Date	Country	Organisation	Type of Organisation	Comment number
17.01.2024	France	Task Force (Adama, Albaugh, Bayer, Nufarm)	Company-Manufacturer	15
Comment received				
Tebuconazole Task Force does not agree with the proposal of classification for fertility and developmental toxicity in category 1B (page 86). As there appears to be a disproportionate emphasis on publications (regardless of their reliability) over standard studies (GLP and OECD),				

we are of the opinion that a revision is needed to take all the scientific information into consideration in a well-balanced weight of evidence.

More information is provided in the attached document. Please see further explanations in the attached document “Tebuconazole_Commenting table_CLH_report_20240116_sanitised”.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tebuconazole_Commenting table_CLH_report_20240116_sanitised.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Tebuconazole_Commenting_tables.zip

Date	Country	Organisation	Type of Organisation	Comment number
10.01.2024	Germany		MemberState	16

Comment received

Adverse effects on sexual function and fertility
The classification proposal is supported.
In various studies a prolonged gestation, dystocia and effects on the reproductive system of males (exposed during puberty) have been detected without pronounced general toxicity. Furthermore, tebuconazole is an aromatase inhibitor reducing levels of reproductive hormones. There is clear evidence of an adverse effect on sexual function and fertility, which justifies a classification as Repr. 1B, H360F.

Adverse effects on development
Tebuconazole has been investigated in various developmental toxicity studies in mice, rats and rabbits. Increased incidences of external malformations (e. g. cleft palates, open eyes), perinatal death, postimplantation loss and reduced foetal and pup growth have been observed. These effects cannot be attributed solely to non-specific maternal toxicity. In addition, tebuconazole was identified as an aromatase inhibitor having an influence on levels of reproductive hormones. Overall, there is clear evidence of developmental toxicity, which justifies a classification as Repr. 1B, H360D.
In total, the severity of the effects for fertility and those observed for development justify a classification as Repr. 1B, H360FD.

Date	Country	Organisation	Type of Organisation	Comment number
08.01.2024	Sweden		Individual	17

Comment received

The guideline DNT study of tebuconazole indicates effects at all dose levels tested, including effects on motor activity, auditory startle, brain weight and brain measurements. This could further support a classification as Repr. 1b for effects on development.

The Developmental Neurotoxicity (DNT) Study (2000, Reference Vol 3 B.6.6.2.1.2/01), compliant to a U.S. EPA guideline, tested dietary dose levels of 100, 300 and 1000 ppm in rats. According to the original study report as well as the CLH report (p. 62 + 63), the offspring NOAEL was 300 ppm.

The U.S. EPA, in their evaluation of the same study, identified instead an offspring LOAEL at 100 ppm, while the NOAEL was not observed.

It should be evaluated if the conclusions drawn by the U.S. EPA should be applied in the EU

as well. (The detailed evaluation by RMS of this study is not available to me.)

I paste the overall conclusion regarding offspring effects from the U.S: EPA's evaluation: "The LOAEL for offspring toxicity is 100 ppm based on decreases in body weights, decreases in absolute brain weights and measurements, and decreases in motor activity. The NOAEL is not determined."

For details, I refer to the Data Evaluation Record by the U.S. EPA (2000), available on p. 482 from https://www.regulations.gov/document/EPA-HQ-OPP-2016-0093-0183

I would like to highlight that according to EU law, in particular Regulation 283/2013 Annex, Introduction, point 1.2, the applicant companies were likely under obligation to inform RMS of the assessment by U.S. EPA: "Any information on potentially harmful effects of the active substance (…) on human and animal health (…) shall be included." Probably, the applicant companies should have informed RMS of the EPA's assessment already during the previous EU evaluation.

In addition, the U.S. EPA has identified an apparent selection of rat brains for morphometrics measurements in this DNT study that may have masked more severe effects: "It appears that the brains evaluated for morphometrics were not entirely representative of the treatment group. If the control brains chosen for morphometric analysis had been more representative, it is possible that larger treatment-related differences in morphometric measures would have been seen." (p. 510 in EPA document cited above) RMS should consider if this represents a potential violation of GLP requirements, in so far as the study report specifies that rats evaluated for morphometrics were randomly chosen. If so, a study audit should be considered.

HEALTH HAZARDS – Specific target organ toxicity - single exposure

Date	Country	Organisation	Type of Organisation	Comment number
17.01.2024	France	Task Force (Adama, Albaugh, Bayer, Nufarm)	Company-Manufacturer	18
Comment received				
We agree with the proposal that no classification is required for specific target organ toxicity- single exposure (page 92). ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tebuconazole_Commenting table_CLH_report_20240116_sanitised.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Tebuconazole_Commenting_tables.zip				

HEALTH HAZARDS – Specific target organ toxicity - repeated exposure

Date	Country	Organisation	Type of Organisation	Comment number
10.01.2024	Germany		MemberState	19
Comment received				
Tebuconazole has been tested in several studies in rats, mice, rabbits and dogs. Effects on the liver, the spleen, the adrenals and the eyes have been observed. With respect to classification and labelling the effects on the eyes in dogs at doses below the guidance value should be considered most relevant. As no mechanistic information was provided showing non-relevance of the effects for humans, cataract formation in dogs in the 90-day and 1-year studies is currently considered relevant for classification and labelling. A classification				

as STOT RE 2 (eyes) is justified.

Date	Country	Organisation	Type of Organisation	Comment number
17.01.2024	France	Task Force (Adama, Albaugh, Bayer, Nufarm)	Company-Manufacturer	20
Comment received				
We do not share the opinion that a classification as STOT RE 2 for the eye is justified based on the available data (page 106). Indeed, the eye effects observed at dose below the guidance value for STOT RE 2 (i) did not progress to severe stage, (ii) were not correlated with histopathological findings, (iii) were not dose-related (at the higher dose, only one animal was transitory affected) and (iv) some incipient lens stars were also observed in various animals regardless of the groups concerned before start of study. Therefore, since significant and severe effects on the eyes were detected only above the STOT-RE 2 classification cut-off levels, we are of the opinion that tebuconazole does NOT meet the criteria for classification for specific target organ toxicity-repeated exposure. Please see further explanations in the attached document “Tebuconazole_Commenting table_CLH_report_20240116_sanitised”. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tebuconazole_Commenting table_CLH_report_20240116_sanitised.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Tebuconazole_Commenting_tables.zip				

Date	Country	Organisation	Type of Organisation	Comment number
18.01.2024	Germany	<confidential>	Company-Manufacturer	21
Comment received				
Although the respective dog studies are included in the BPR dossier for the renewal of the approval of tebuconazole, during the previous evaluation steps since the submission in 2018, this classification has never been a topic for discussion. The comments’ submitter is therefore surprised that DK-RMS now considers a STOT RE 2 (eyes).				

HEALTH HAZARDS – Aspiration hazard

Date	Country	Organisation	Type of Organisation	Comment number
17.01.2024	France	Task Force (Adama, Albaugh, Bayer, Nufarm)	Company-Manufacturer	22
Comment received				
We agree with the proposal “not applicable” for aspiration hazard (page 106). ECHA note – An attachment was submitted with the comment above. Refer to public attachment Tebuconazole_Commenting table_CLH_report_20240116_sanitised.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Tebuconazole_Commenting_tables.zip				

PUBLIC ATTACHMENTS

1. Tebuconazole_Commenting table_CLH_report_20240116_sanitised.pdf [Please refer to comment No. 1, 4, 5, 6, 7, 8, 9, 10, 15, 18, 20, 22]

CONFIDENTIAL ATTACHMENTS
1. Tebuconazole_Commenting_tables.zip [Please refer to comment No. 1, 4, 5, 6, 7, 8, 9, 10, 15, 18, 20, 22]