Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

biphenyl-2-ol; 2-phenylphenol; 2-hydroxybiphenyl

EC Number: 201-993-5
CAS Number: 90-43-7

CLH-O-0000007210-88-01/F

Adopted

1 December 2022

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BIPHENYL-2-OL; 2-PHENYLPHENOL; 2-HYDROXYBIPHENYL

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during 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 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 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. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: biphenyl-2-ol; 2-phenylphenol; 2-hydroxybiphenyl
EC number: 201-993-5
CAS number: 90-43-7
Dossier submitter: Spain

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
26.04.2022	Germany	LANXESS Deutschland GmbH	Company-Manufacturer	1
Comment received				
In our comments the term "OPP" is used as a synonym for biphenyl-2-ol resp. 2-phenylphenol. Section 2.10.1, Table 2.10.1: It is not justified to rank the female and male PP assays as "supportive". The main reasoning is that the mid-dose level was set to 250 rather than 450 mg/kg bw/d (50% of high dose) as stipulated by the respective OPPTS guidelines. This is only a minor deviation from the guideline. The choice of the mid-dose does not affect the conclusion that the highest dose of 900 mg/kg bw/day did not cause significant ED-related effects. We also do not agree that the MTD was exceeded. Ranking a study as "supportive" suggests that the study cannot be used to conclude on its respective endpoint. This is not the case as the study shows the absence of EAS-related effects in prepubertal rats. The observed change of oestrous cycling in the high-dose females reflects normal biological fluctuation. Furthermore, such a change was not seen in any of the two 2-generation studies, nor was a functional effect on female fertility observed in these studies. The DS indicates in B.6.8.3-09 that the MTD was exceeded, and this is one of the reasons that the study was graded as only supportive. However, MTD is conventionally defined as the highest dose to produce toxic effects without causing death and to decrease body weight gain by no more than 10% relative to controls. There were some deaths in each of the treatment groups. These findings were identified as isolated occurrences deemed unrelated to OPP. Therefore, none of these deaths were attributed to toxicity related to OPP treatment. The EPA test guideline also states that increases in BUN might indicate that the MTD has been exceeded: "In well-controlled toxicity studies in				

rodents, relatively small increases in serum BUN and creatinine concentrations (e.g., 1.5-fold) can be indicative of renal injury but significant and consistent increases in BUN or creatinine above control ranges, including laboratory reference ranges, provide more support for a treatment related effect". However, BUN values of KCA 5.8.3-08 (reported in B.6.8.3-08) are: BUN at 900 mg/kg bw/day = 16 mmol/L; BUN control = 13 mmol/L. Historical control = 12 (range not given). Therefore, concurrent control already in exceedance of HCD. This would therefore require a BUN of 19.5 mmol/L to be considered indicative of renal injury (i.e., ≥1.5x increase). BUN values of KCA 5.8.3-09 (reported in B.6.8.3-09) are: BUN at 900 mg/kg bw/day = 19 mmol/L; BUN control = 15 mmol/L. Historical control = 12-15. a BUN of 22.5 mmol/L would be needed to be considered indicative of renal injury (i.e., ≥1.5x increase). Therefore, it can be concluded that the MTD was not exceeded. Also, the DS indicates that adjustment of all parameters was done to PND23 instead PND21, and animals at the highest dose had minor weight prior the beginning of the study. However, again, this is considered not to be a reason to consider the study to only to be supportive. (However, this is addressed as well in following comments.) In conclusion, the study should be considered acceptable.

Section 2.10.1, Table 2.10.2.1.2
The effects listed in this table should be restricted to T-related effects. The lengthy listing of general toxicity effects and unrelated organ weights etc. make the table very hard to work with.

Section 2.10.1, ED assessment for EAS-modalities, p.273
The DS concludes that EAS-mediated parameters were not sufficiently investigated. However, the WoE of the Level 2, 3, and 4 studies clearly show the absence of EAS-related activity: pro-estrogenic UT-assay negative, ToxCast anti-ER model negative, ToxCast steroidogenesis assays negative, ToxCast AR model (pro- and anti-androgenic) negative. Male and female PP assays were also negative.
The current interpretation by EFSA is that pre-2001 two-generation studies are an "insufficient investigation" of EAS parameters and adversity level. However, the available in-vitro and in-vivo mechanistic studies (level 2, 3, and 4) demonstrate the absence of relevant endocrine activity. By definition, a positive Hershberger assay requires at least two organ weights to be significantly changed, which was not the case. Following the decision tree of the ED guidance, this leads to Scenario 2a(ii). ED criteria are not met, and no further studies are required. The RAR should also appreciate the negative ToxCast AR models for both up- and down-regulation of AR (only the ToxCast ER models are mentioned). The ToxCast models integrate the results from various assays. The AUC for AR-assays was zero.

Section 2.10.1, ED assessment for EAS-modalities, Table 2.10.2.2.2.1/1 & Vol. 3 Section B.6.8.3-08
The DS indicates that regular cycling was altered at 900 mg/kg bw/day (dose above MTD) in study B.6.8.3-08. However, the observed change of oestrous cycling in the high-dose females assay reflects normal biological fluctuation and was consistent with historical control data. Additionally, the MTD was not exceeded as only one female died at 900 mg/kg bw/day and this was due to accidental lung dosing.
Changes in oestrous cycling were only observed in the female PP but not in the 2 available OECD 416 studies. irregular cycling being normal biological fluctuation is normal in young rats as also reported by Stump et al. (2014) stating: "It is not uncommon for young animals to cycle abnormally with the initiation of estrous cycling (it usually takes until about 8 weeks of age for normal cycles to occur consistently) …" This applies to the pubertal assay where animals are younger than 8 weeks. (Stump et al., 2014. Key Lessons from Performance of the U.S. EPA Endocrine Disruptor Screening Program (EDSP) Tier 1 Male and

Female Pubertal Assays Birth Defects Res B Dev Reprod Toxicol. 2014 Feb;101(1):43-62. doi: 10.1002/bdrb.21097.)

Section 2.10.1, ED assessment for EAS-modalities, Table 2.10.2.2.2.1/2
The DS mentions the in-vitro aromatase inhibition by OPP (only top concentration with above 50% inhibition) and the increase of in-vitro oestradiol synthesis without discussing that both results are conflicting. The occurrence of irregular oestrus cycling in high-dose females in the PP study is over-interpreted. Aromatase inhibition should lead to a decrease of oestradiol, not an increase. Apical endpoints that are sensitive to oestradiol like VO or age at first oestrus were not affected by OPP up to 900 mg OPP /kg bw/d. Figure 6.8.3-08/1 shows that historical control groups often showed an irregular pattern of oestrus cycle which is common in young animals as also reported by Stump et al., 2014.

Section 2.10.1, Point 2.2.4.2 Further information to be generated to postulate MoA
The DS does not acknowledge the overwhelming WoE that OPP has no endocrine activity in vivo, inter alia demonstrated by the combination of Hershberger, UT, and male/female PP assays. Instead, isolated findings like high-dose anti-androgenic activity or pituitary wt changes are pointed out, although these have no conclusive pattern. The recommendation to conduct a new OECD 416 or 443 study is therefore disproportionate.
A perturbation of the hypothalamic–pituitary–adrenal axis is discussed but most available studies showed no effects on the weight or histology of pituitary and adrenal glands. The mentioned brain effects are restricted to organ weight changes with concomitant BW depression. In addition, anti-androgenic effects cannot only be detected via AGD decrease and nipple retention in males but can also be analysed by the following parameters: decreased reproductive organ weights and/or histopathological changes, undescended testes, decreased male fertility, delayed puberty onsets, penile malformations (e.g. hypospadias).
The available data, including two OECD 416 studies (KCA 5.6.1-01 & KCA 5.6.1-02) do not support any anti-androgenic mediated adversity since:
No statistically significant alterations were observed in testicles, epididymides, prostate and pituitary.
External examination did not show malformations, mating & fertility were not altered.
No effect on absolute testes weights in P and F1 parents.
No significant delay in pubertal onset (BPS) when considering body weight at BPS.
No effect on male mammary gland histopathology in mouse, rat, and dog chronic studies.
Therefore, the dataset including two multigeneration studies performed according to former OECD 416, a uterotrophic assay in ovariectomised rats, negative ToxCast Model data for estrogen antagonism, Hershberger assay, and a pubertal development and thyroid function assay in intact juvenile/peripubertal male and female rats, provides a significant weight of evidence on the EAS modalities.

Vol. 3, B.6.8.3, Table 6.8.3-07/5
The DS states that ventral prostate weight is especially sensitive to interference with 5α-reductase. This is an isolated finding that is not corroborated by at least a second significant weight change. This is the criterion for a positive test laid down in OECD TG 441 and this is not fulfilled.
An anti-androgenic effect of OPP was not observed in any other AR-reporter-gene assays (ToxCast model AUC=0), despite the long incubation times (≥20 h) and the lack of detoxification by conjugation in these test systems in contrast to in-vivo models.

Vol. 3, B.6.8.3-09
The DS states that BPS was adjusted to PND23, but the ANCOVA used BW @ PND22 as covariate. This is one day later than suggested by the guideline, but Table 6.8.3-09/3.1

clearly shows that control and high-dose animals essentially weighed the same when BPS occurred. This is more informative than correcting for a BW that was measured 3 weeks before this event. Using BW @ PND22 as covariate does not justify ranking this study as merely "supportive".

Vol. 3, B.6.8.3-01 In vitro and in silico mechanistic data: US EPA EDSP21
Details on data and DS conclusion should be amended. E-Modality: for the QSAR models (Table B.6.8.3-01/3: Consensus CERAPP QSAR ER Model Predictions, Vol. 1 Table 2.10.2.2.2.1/2) it should be mentioned that there is no information on the applicability domain and thus on the reliability of the QSAR. In the DS conclusion, it should be noted that the ER ToxCast Model prediction is negative for antagonism (being considered sufficient information based on the ECHA/EFSA ED Guidance).
A-Modality: For completeness, the AR ToxCast prediction model should be reported which is negative (AUC=0) for both agonistic and antagonistic activity.

Vol. 1, Table 2.10.1
The acceptability of in-vitro high throughput screening data from EPA CompTox database should be considered as "supporting" and not "acceptable".

Volume 1, Table 2.10.2.2.2.1/2
For the in-silico model cited (CERAPP) no information on applicability domain is available and thus reliability of this supporting information is unclear. Moreover, it should be added that the ER ToxCast Model prediction is negative (AUC=0) for antagonistic effects.

Volume 1, 2.2.4 MoA analysis for EAS modalities
Volume I on page 335, 2.2.4, it is stated "…the importance of the 5α-reductase alteration, AOP pathway 288 (from AOP wiki) relates…". However, this AOP cited from AOP wiki does not relate to 5α-reductase but to inhibition of 17α-hydrolase/C 10,20-lyase (Cyp17A1) activity.
AOPs listed on AOP wiki related to 5α-reductase inhibition and currently under development are:
a) ID 305: 5α-reductase inhibition leading to short anogenital distance (AGD) in male (mammalian) offspring
b) ID 289: Inhibition of 5α-reductase leading to impaired fecundity in female fish
c)ID 120: Inhibition of 5α-reductase leading to Leydig cell tumors (in rat)

AOP 305: AO is not observed, since the AGD was not analysed in available data.
AOP 289: Some indications for decreased fecundity in female fish at high doses were observed in a short-term reproduction study (KCA 8.2.2.1/01) and in the FSTRA (KCA 8.2.3/01). However, KE 4 of the AOP 289 (decrease in plasma vitellogenin concentrations) is neither observed in the short-term reproduction study (KCA 8.2.2.1/01) nor in the FSTRA (KCA 8.2.3/01). Since KE are essential for the AO, AOP 289 is not supported by the available data.
AOP 120: Leydig cell hyperplasia and following increase in Leydig cell tumour incidence were not observed in the available subchronic and chronic/carcinogenicity studies performed with OPP where testes histopathology was performed. Additionally, in the 2-generation studies no effects on testes histopathology were observed.
In conclusion, when considering the available information from existing mammalian and fish studies, there is no indication for 5α-reductase inhibition and related adverse effects.

Volume 1, Table 2.10.2.2.1
In Volume I on page 274, Table 2.10.2.2.1 it is stated "EAS-mediated parameters not measured" whereas above the respective table it is stated "There are parameters related to

endocrine activity that have not been measured, as it is indicated in Table 2.10.2.2.1". Both statements should be reworded since the table contains "in vivo mechanistic" and "EATS-mediated" parameters. Moreover, the statement on gestation length under OECD 414 should be removed.
Moreover, in this Table it is stated that "gestation length" is a missing parameter for OECD TG 414. However, gestation length is no common parameter in pre-natal developmental toxicity studies since gestation is ended with caesarean section according to OECD TG 414.
Additionally, the parameter "genital abnormalities" is reported as missing. However, foetuses were examined and thus "genital abnormalities" would have been reported if present.

Volume 1, Table 2.10.2.2.2
In Volume I on page 275, Table 2.10.2.2.2 it is stated "evidence of EAS mediated activity from in vitro studies. In vivo studies also indicate alterations, as observed". We do not agree that endocrine activity was observed in vivo based on the available dataset.
Moreover, it is stated "Some evidence of endocrine activity is observed, including ToxCast estrogen model, ER and AR binding assays and aromatase / steroidogenesis assays, which gave positive or equivocal results" Equivocal test results as of the ToxCast ER antagonism model should not be reported as evidence for activity.
Moreover, it should clearly be stated that the E-modality is sufficiently investigated showing negative results in the UT assay as well as the ToxCast ER prediction model for antagonistic effects.
It should also be noted that ToxCast high throughput in vitro data is "supportive" whereas in vivo and in vitro Guideline studies are "acceptable".

Volume 1, Table 2.10.2.2.2.1/1
In Volume I on page 328, Table 2.10.2.2.2.1/1 it is stated "Seminal vesicles weight showed an increased weight in the only study it was measured (ID 32, at 900 mg/kg/day above the MTD"
An increase in weight was not reported, more details on organ weight can be found under KCA 5.8.3-08 or the respective summary under Vol. 3 B.6.8.3-09.

Volume 1, Table 2.10.2.2.2.1/1; Volume 1 2.2.4
In Volume I on page 328, Table 2.10.2.2.2.1/1 and p. 336 it is stated that the fertility index was decreased in study ID 20. However, this is not the case, as all females in all treatment groups were confirmed to be pregnant (by observation of the presence of vaginal plug). The reduced number of litters with live foetuses was due to unscheduled deaths in all treatment groups. Bleeding from the ostium vaginae was found in almost all the mice that died, presumably attributable to abortions (i.e., due to maternal toxicity).
Moreover, in OECD 414 studies, animals are not exposed during mating but only during gestation. Therefore, fertility index (Fertility index (%) = (No. of females pregnant/no. of females with confirmed mating) × 100) is not a relevant parameter to investigate n OECD 414, since the exposure starts after conceiving.

Volume 1, Table 2.10.2.2.3
In Volume I on page 334, Table 2.10.2.2.3 it is stated that a MoA is required (scenario 2a (i)) since endocrine activity was observed. However, the correct scenario to be chosen based on the WoE on available data is scenario 2a (iii). In general, we do not agree that further data are needed to conclude on the absence of EAS-related endocrine disrupting properties of OPP based on the available dataset which shows no EAS-mediated adversity.
It is acknowledged that the available OECD 416 studies do not include all EAS-mediated parameters required according to the ED Guidance but the dataset is completed with in vitro and in vivo data on endocrine activity where no relevant effect was observed in vivo.

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ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CONFIDENTIAL_Attachm_New_Muta_Studies_LANXESS.7z

Dossier Submitter's Response

Company's comments are focused on the ED assessment. The DS would like to note that the endocrine disruption (ED) properties of 2-phenylphenol will be discussed in the context of the renewal of the active substance under Regulation 1107/2009 (PPP) in the EFSA Pesticides Peer Review Expert's Meeting (PREV). From our understanding ED is out of the scope of the harmonization fo classification and labelling (CLH) according to CLP Regulation. However, the adversity of some of the effects noted by the Company could be regarded for the corresponding hazard class according to CLP. It has to be noted that the DS has not proposed classification according to CLP for STOT RE, STOT SE or reprotoxicity.

Section 2.10.1, Table 2.10.1: Ranking prepubertal assays as "supportive"

The main reasoning of the DS to consider both studies as supportive is that maximum tolerated dose (MTD) was exceeded at the highest tested dose level of 900 mg/kg bw/day. This statement was supported by the toxic effects observed at this dose level:

Pubertal assay in female rats (B.6.8.3-08): significant increases in BUN (23%), alanine aminotransferase (102%), phosphorus (14%), and kidney effects in histopathology including necrosis.

Pubertal assay in male rats (B.6.8.3-09): decreased body weights (11.6%) and body weight gain (12.6%), increased liver weights (21% in relative liver weight and increase of adjusted (for PND 23) weight of 10%), increased BUN (27%) and kidney effects seen in histopathology.

According to the DS, the pattern of toxic effects seen in both studies indicates that MTD was exceeded. This is an important limitation for both studies which do not allow to accurately assess the parameters measured. This problem with the highest tested dose level would be less relevant if ED-related effects had not been observed in the studies. However, the DS considers relevant the effects seen at 900 mg/kg bw/day:

Pubertal assay in female rats (B.6.8.3-08): dose dependent decrease in females cycling and an increase in the mean cycle length (not statistically significant).

Pubertal assay in male rats (B.6.8.3-09): unadjusted age of balanopreputial separation was significantly increased (45.2 vs 43.1) at 900 mg/kg/day. In addition, weights of seminal vesicles plus coagulating gland with fluid, ventral prostate, LABC, left testis and left and right epididymis were decreased significantly at the dose of 900 mg/kg/day.

Section 2.10.1, Table 2.10.2.1.2

DS does not agree with the Company comment. According to the ECHA-EFSA ED Guidance (2018), in the integration of the lines of evidence in a tabular format, "Additional information, e.g. on systemic general toxicity or other target organ effects, may be used at this point, on a case-by-case basis, in order to contextualise the presence or absence of an adverse effect potentially linked to an endocrine activity." Indication of general systemic toxicity should also be reported in this table to allow the assessment of potential secondary effects.

Section 2.10.1, ED assessment for EAS-modalities, p.273

It has to be noted that the endocrine disruption properties of 2-phenylphenol will be discussed in the scope of the EFSA Pesticide Peer Review Expert Meeting. In any case, the DS does not agree with the Company view focused on the absence of EAS-related activity.

According to the ED assessment several in vitro and in vivo mechanistic studies show alterations: ER binding assay (B.6.8.3-02, equivocal result), AR binding assay (B.6.8.3-03, positive result), aromatase assay (B.6.8.3-04, inhibition of the enzyme), steroidogenesis (B.6.8.3-05, positive result), Hershberger assay (B.6.8.3-07, significantly alteration of ventral prostate weight) and pubertal assay in female and male rats (B.6.8.3-08, and B.6.8.3-09, respectively), where different types of alterations are observed, including oestrous cycle irregularities and delay of balanopreputial separation (at doses above MTD).

With respect to the Company interpretation of the Hershberger study results (B.6.8.3-07), the DS is of the opinion that the observed decrease of ventral prostate weight at 1000 mg/kg bw/day + TP (28%) should not be ruled out since this tissue is especially sensitive to substances that are able to interfere with 5α-reductase. Although only the ventral prostate showed a statistically significant decrease in weight, all target tissues displayed some degree of reduced growth.

Finally, Toxcast AR models showed no activity. However other positive results were seen for the A-modality in the androgen receptor assay and also in the Hershberger study as it has been previously commented.

Section 2.10.1, ED assessment for EAS-modalities, Table 2.10.2.2.2.1/1 & Vol. 3 Section B.6.8.3-08

Data available in the pubertal female study (B.6.8.3-08) indicate at 900 mg/kg bw/day a significant reduction in the regularity of cycling (28.6% vs 86.7% of controls) and a non-significant increase in the cycle length (5.7 days vs 4.7 days in controls). The US EPA 890.1450 states that 'regularity of cycling should be given more weight than lack of statistical significance for the difference in weight of ovary or uterus in treated animals compared to controls'.

Consequently, the DS is of the opinion that this effect should be considered for the assessment of ED and also for reproductive toxicity though it has to be noted that MTD was exceeded in this study.

Section 2.10.1, ED assessment for EAS-modalities, Table 2.10.2.2.2.1/2

Aromatase in vitro inhibition was seen in the available study (B.6.8.3-04) and also an increase in the in vitro oestradiol synthesis observed in the steroidogenesis assay (B.6.8.3-05). However, the DS does not agree with the Company view of the pubertal female study (B.6.8.3-08) outcome in which at 900 mg/kg bw/day (above MTD according to DS) a significant reduction in the regularity of cycling (28.6% vs 86.7% of controls) and a non-significant increase in the cycle length (5.7 days vs 4.7 days in controls) was seen. The US EPA 890.1450 states that 'regularity of cycling should be given more weight than lack of statistical significance for the difference in weight of ovary or uterus in treated animals compared to controls'. This effect could be relevant for the assessment of the reproductive toxicity.

Section 2.10.1, Point 2.2.4.2 Further information to be generated to postulate MoA

ED assessment included in the RAR corresponds to an interpretation of available data for 2-phenylphenol according to the EFSA-ECHA ED guidance (2018).

Inconsistencies/uncertainties have been underlined to be posed and possibly clarified during the EFSA PREV meeting in which the DS recommendation to conduct new studies will be discussed. This is only the DS view.

Vol. 3, B.6.8.3, Table 6.8.3-07/5

ED assessment included in the RAR corresponds to an interpretation of available data for

OPP according to the EFSA-ECHA ED guidance (2018). Inconsistencies/uncertainties have been underlined to be posed and possibly clarified during the EFSA PREV meeting in which the DS recommendation to conduct new studies will be discussed. This is only the DS view.

Vol. 3, B.6.8.3-09
Thanks for the clarification on the BPS adjustment to PND22 instead of PND23 although it was one day later than PND 21 as included in the guideline. Additionally, the DS underlines that the ranking of this study of supportive was mainly based on the toxic effects seen at the highest tested dose level of 900 mg/kg bw/day indicating that the maximum tolerated dose (MTD) was exceeded. This excessive dose level jeopardised the results of the study.

Vol. 3, B.6.8.3-01 In vitro and in silico mechanistic data: US EPA EDSP21
Consensus CERAPP QSAR ER Model Predictions was included in the ED Assessment as additional data but it has to be noted that it is not an alternative or substitute to the ER ToxCast required according to the ECHA-EFSA ED Guidance (2018) and available for the active substance. Consequently, CERAPP data is only supportive to ER Toxcast Model.
It is indicated in the summary of Vol.3 B.6 that the ER ToxCast Pathway Model (AUC) was negative for antagonism
AR Toxcast prediction model is included in Volume 3 and according to Table 2.10.2.2.2: there was no effect for agonism/antagonism

Vol. 1, Table 2.10.1
Consensus CERAPP QSAR ER Model Predictions was included in the ED Assessment as additional data but it has to be noted that it is not an alternative or substitute to the ER ToxCast required according to the ECHA-EFSA ED Guidance (2018) and available for the active substance. Consequently, CERAPP data is only supportive to ER Toxcast Model.

Volume 1, Table 2.10.2.2.2.1/2
It is indicated in the summary of Vol.3 B.6 that the ER ToxCast Pathway Model (AUC) was negative for antagonism

Volume 1, 2.2.4 MoA analysis for EAS modalities
The reference to AOP pathway 288 is not correct as indicated by the Company.

Volume 1, Table 2.10.2.2.1
The title of Table 2.10.2.2.1 should have incuded the following: in vivo mechanistic and EATS mediated parameters. The DS agrees in which aestation length and genital abnormalities should be out of this table.

Volume 1, Table 2.10.2.2.2
According to the DS, ED assessment of several in vitro and in vivo mechanistic studies show alterations: ER binding assay (B.6.8.3-02, equivocal result), AR binding assay (B.6.8.3-03, positive result), aromatase assay (B.6.8.3-04, inhibition of the enzyme), steroidogenesis (B.6.8.3-05, positive result), Hershberger assay (B.6.8.3-07, significantly alteration of ventral prostate weight) and pubertal assay in female and male rats (B.6.8.3-08, and B.6.8.3-09, respectively), where different types of alterations are observed, including oestrous cycle irregularities and delay of balanopreputial separation (at doses above MTD).
Since EAS-mediated activity has been observed, but EAS- mediated adversity has not been sufficiently investigated, the relevant scenario for the ED assessment of EAS-modalities corresponds to a scenario 2a (i): Perform MoA analysis (additional information may be

needed for the analysis).

Volume 1, Table 2.10.2.2.2.1/1
The sentence contains a typo. The correct sentence is Seminal vesicles weight showed a decreased weight in the only study it was measured (ID 32, at 900 mg/kg/day above the MTD.

Volume 1, Table 2.10.2.2.2.1/1; Volume 1 2.2.4
According to the DS assessment EAS-mediated activity has been observed, but EAS-mediated adversity has not been sufficiently investigated, corresponding to a scenario 2a (i). In this case further data need to be generated to perform a MoA. It is considered that more information from a level 5 study is needed. Specifically, a Two-Generation Reproduction Toxicity Study (OECD 416) or an Extended One-Generation Reproductive Toxicity Study (OECD 443) should be conducted (the latter would be preferred). This proposal is only the DS opinion.

Volume 1, Table 2.10.2.2.3
According to the DS assessment EAS-mediated activity has been observed, but EAS-mediated adversity has not been sufficiently investigated, corresponding to a scenario 2a (i). In this case further data need to be generated to perform a MoA. It is considered that more information from a level 5 study is needed. Specifically, a Two-Generation Reproduction Toxicity Study (OECD 416) or an Extended One-Generation Reproductive Toxicity Study (OECD 443) should be conducted (the latter would be preferred).

RAC's response

Thank you very much for your comments. RAC notes that endocrine disruption as such is not target of the Regulation (EC) N° 1272/2008 and therefore these comments are not relevant for classification purposes.

Date	Country	Organisation	Type of Organisation	Comment number
27.04.2022	Germany		MemberState	2

Comment received

see attachment

ECHA note – An attachment was submitted with the comment above. Refer to public attachment DE-CA_Comments_CLH-biphenyl-2-ol_2-phenylphenol_2-hydroxybiphenyl_non_conf.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment DE-CA_Comments_CLH-biphenyl-2-ol_2-phenylphenol_2-hydroxybiphenyl_final.pdf

Dossier Submitter's Response

The sodium salt is covered for the renewal of the active substance according to Regulation 1107/2009 (PPP) but is not addressed for the harmonised classification and labelling (CLH) according to CLP Regulation.

RAC's response

Thank you very much for your comments. RAC notes that sodium OPP salt is not targeted in this proposal of classification and made its assessment considering only information for OPP as such, because there are enough information for such purpose.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
26.04.2022	Germany	LANXESS Deutschland GmbH	Company-Manufacturer	3

Comment received

Section 2.6.5.2
The bladder tumours that are critical for the suggested Carc 2 classification are very clearly specific to a single sex (male) and a single species (rat, but not mouse, dog, hamster, or guinea pig). The relevance of the proposed MoA cannot be excluded with absolute certainty, which can never exist. However, the proposed MoA is certainly not relevant for humans at doses that are associated with the proposed uses of OPP. The analogy to Na saccharine and Na ascorbate is striking. No classification for carcinogenicity is warranted.

Section 2.6.5.2, p.130
The DS states that "[t]he fact that high systemic OPP doses are necessary [..] bears no relevance as to the specificity of this MoA to the rat." While it is conceivable that an overload of OPP-detoxification could eventually cause urinary bladder effects in humans, it must be recognised that such the necessary doses cannot be reasonably achieved by any foreseeable exposure scenario. Overload situations are artefactual and not relevant for human risk assessment. This is very similar to the fosetyl precedence case in which the practically non-attainable tumorigenic doses have averted a Carc2 classification. It would be fair to adapt the same logic to OPP. Please refer for a comparison to: EFSA (2018, amended 8 March 2019). Peer review fo the pesticide risk assessment of the active substance fosetyl. EFSA Journal 2018; 16(7): 5307.

Section 2.6.5.2, p.131
The DS states that "[t]he fact that the pH and sodium concentration of human urine is lower than in rat urine does not make the suggested MoA rat specific either." Nonetheless, this inter-species difference of urine composition was recognised as the key for human non-relevance of the bladder tumours in male rats caused by sodium ascorbate and sodium saccharine (cf. Fukushima et al., 1986; B.6.8.2-10).

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Public Attachments_LANXESS.7z
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CONFIDENTIAL_Attachm_New_Muta_Studies_LANXESS.7z

Dossier Submitter's Response

The DS agrees with the applicant that tumours are observed in one sex and one species only and, as it was stated in the CLH proposal, this drove the DS to consider them as limited evidence of carcinogenic potential and to propose a classification as Carcinogen category 2.
In the opinion of the DS. the absolute certainty about the MoA is not required to dismiss the human relevance of the tumours, but a more solid argumentation would be necessary (i.e., demonstration of the key events of the proposed adverse outcome pathway, analysis of the dose-response concordance, temporal association of the events, analysis of the plausibility of the proposed MoA, a comparative description of alternative MoA and uncertainties, inconsistencies and data gaps of the postulated MoA).
In the absence of a more complete analysis of the MoA by which biphenyl-2-ol generates tumours in the urinary bladder of male rats and a more substanciated comparison to the human case, the DS proposes the classification as of this substance as Carcinogen category 2 ("suspected human carcinogen").

RAC's response
Thank you very much for your comments. RAC notes all the appointed arguments and will consider them in the weight of evidence assessment.

Date	Country	Organisation	Type of Organisation	Comment number
27.04.2022	Germany		MemberState	4
Comment received				
see attachment ECHA note – An attachment was submitted with the comment above. Refer to public attachment DE-CA_Comments_CLH-biphenyl-2-ol_2-phenylphenol_2-hydroxybiphenyl_non_conf.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment DE-CA_Comments_CLH-biphenyl-2-ol_2-phenylphenol_2-hydroxybiphenyl_final.pdf				
Dossier Submitter's Response				
The DS appreciates the comment in support of the evaluation of the substance.				
RAC's response				
Thank you very much. Noted.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
26.04.2022	Germany	LANXESS Deutschland GmbH	Company-Manufacturer	5
Comment received				
Section 2.6.4, Table 50, Sections 2.6.4.1, 2.6.4.2, and 2.6.4.3 A new Ames test and a new in-vitro micronucleus assay have been conducted with OPP. The new tests were both negative and were conducted to overcome deficiencies in the available tests for each endpoint and to reflect to current specification of OPP. Both study summaries are submitted in the public attachment. File name: OPP_Section 10_8_CLH report_Muta_Public Attach.pdf. Please refer also to the confidential attachment. The in-vitro MNT can detect structural and numerical aberrations. Due to its static exposure conditions, it is considered more sensitive than an in-vivo MNT in which a large proportion of OPP is rapidly detoxified and excreted. Furthermore, the negative in-vitro MNT supports negative in-vivo cytogenetic studies with OPP in bone marrow and urinary bladder. This allows the conclusion that OPP is not genotoxic which should be the conclusion of this section. The studies by Tayama et al. (1989) and Tayama & Nakagawa (1991) have been evaluated as "acceptable" despite their severe deficiencies. Most importantly, no proper evaluation of cytotoxicity has been performed in either study. The reduction of DSCs suggests cytotoxicity at all tested OPP concentrations (invalid test system). The studies should be ranked as "not acceptable". Vol.3, B.6.4.2.2-01, pp. 199-201 The in-vivo Comet assay conducted in 2000 was assessed as being "supporting information" only. The study was conducted according to a well-documented method. The deviations from the current guideline are minor. The study is valid and acceptable. The negative result is supported by the negative comet assay with SOPP that was assessed as acceptable. The potential irritant effect of viscous vehicles on sites of first contact is not relevant since				

kidney and liver are not sites of first contact with the dosing solution. Regarding the single versus ≥2 treatments required by the TG 489: OPP has a very short biological half-life in mice (96% excretion via urine within 24 h after oral dosing; cf. B.6.1.1-05). Therefore, a second dosing will not add up to the previous dosing but will be an independent acute event. The sensitivity of the test method was demonstrated by an appropriate positive control, even though the current guideline foresees a higher number of cells (150 instead of 100). The lack of historical data is inevitable for test methods that were new and non-standard at the time and does not constitute a critical deficiency.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Public Attachments_LANXESS.7z
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CONFIDENTIAL_Attachm_New_Muta_Studies_LANXESS.7z

Dossier Submitter's Response

The new available data include an in vitro bacterial mutation assay and an in vitro micronucleus assay. The outcome of these studies indicate that 2-phenylphenol does not induce mutagenicity in bacteria and does not induce micronuclei in vitro. With the new information available, the genotoxicity of 2-phenylphenol may be concluded.
In the absence of a suitable standard measurement of cytotoxicity, the study by Tayama et al. (1989) will be deemed as supporting information and this deviation will be regarded in the deviations from the current guideline.

RAC's response

Thank you very much for your comments. RAC notes the two new studies and will include them in the weight of evidence assessment.

Date	Country	Organisation	Type of Organisation	Comment number
27.04.2022	Germany		MemberState	6

Comment received

see attachment

ECHA note – An attachment was submitted with the comment above. Refer to public attachment DE-CA_Comments_CLH-biphenyl-2-ol_2-phenylphenol_2-hydroxybiphenyl_non_conf.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment DE-CA_Comments_CLH-biphenyl-2-ol_2-phenylphenol_2-hydroxybiphenyl_final.pdf

Dossier Submitter's Response

DS acknowledges DE for the comments and a weight of evidence will be considered to address the genotoxicity of the substance. The applicant has submitted two new mutagenicity studies: one in vitro bacterial mutation assay (Ames test) and one in vitro micronucleus test. The outcome of these studies indicates that 2-phenylphenol is not mutagenic in bacteria and does not induce micronuclei in vitro. In light of the new information available, the genotoxicity of 2-phenylphenol may be concluded.

RAC's response

Thank you very much for your comments. RAC notes the two new studies and will include them in the weight of evidence assessment.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
26.04.2022	Germany	LANXESS Deutschland GmbH	Company-Manufacturer	7

Comment received

Sections 2.6.6.1.1 and 2.6.6.2.1
The DS places great weight on the published re-evaluation by Kwok & Silva (2013). This paper contains factual errors and should not overturn the previous EU evaluations of the available studies. Dr Kwok (as CalEPA assessor) has set the reproductive NOAEL to above 500 mg/kg bw/d. (Cal EPA (2007): Ortho-Phenylphenol (OPP) and Sodium Ortho-Phenylphenate (SOPP). Risk Characterization Document Dietary Exposure. Available online: http://www.cdpr.ca.gov/docs/risk/rcd/opp.pdf)
An expert statement Jenkinson P. (2021) has evaluated the paper by Kwok and Silva (2013). Regarding the two fertility studies, the author concludes that "both studies show, in both the original analysis and the reanalysis of Kwok and Silva, that reproductive toxicity is not observed in the absence of parental toxicity". For the rabbit developmental toxicity studies, Dr Jenkins concludes that "both studies show in the original analysis that developmental toxicity is not observed in the absence of maternal toxicity. The reanalysis of Kwok and Silva purport to show an increase in resorption frequency at a dose level (100 mg/kg/day) where no maternal toxicity was observed. However, careful scrutiny of the data and their observations reveal this to be a statistical artefact without toxicological significance."
The full paper by Dr Jenkins also contains appraisals of other developmental toxicity studies. It is attached as public attachment.
File name: OPP Section 10_10_CLH report_Repro_Jenkinson_2021_Public Attach.pdf

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Public Attachments_LANXESS.7z
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CONFIDENTIAL_Attachm_New_Muta_Studies_LANXESS.7z

Dossier Submitter's Response

DS: The study carried out by Kwok and Silva has been evaluated as reliable study to support reproductive toxicity assessment. The DS acknowledges the applicant´s reply and deemed that some issues should be further discussed.

RAC's response

Thank you very much for your comments. RAC notes the expert position paper provided and will consider all arguments in the weight of evidence during discussion in plenary sessions.

Date	Country	Organisation	Type of Organisation	Comment number
27.04.2022	Germany		MemberState	8

Comment received

see attachment

ECHA note – An attachment was submitted with the comment above. Refer to public attachment DE-CA_Comments_CLH-biphenyl-2-ol_2-phenylphenol_2-hydroxybiphenyl_non_conf.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment DE-CA_Comments_CLH-biphenyl-2-ol_2-phenylphenol_2-hydroxybiphenyl_final.pdf

Dossier Submitter's Response
The DS agrees with Germany in the need of discussion on the increase of resorptions seen in Zablotny et al. (1991c) study at doses ≥ 100 mg/kg bw/day, considering also the re-evaluation of the study performed by Kwok and Silva. The DS did not regard adverse the increases since there was not dose-dependancy, the occurence was also high in concurrent controls and there was not an impact in other indices such as the number of foetuses per litter. The non statistical significance of the effect also supports the lack of adversity, but it has to be noted that the re-evaluation of data performed by Kwok and Silva indicate that resorptions were significant at doses ≥100 mg/kg bw per day. This publication also notes some uncertainties of the study. Moreover, the resorption incidences in both mid and top dose groups were higher than mean and out of the HCD range. HCD was only summarised by Kwok and Silva in their re-evaluation of the study. No more information regarding HCD was provided in the dossier, in the Zablotny et al (1991c) study nor in the Kwok and Silva re-evaluation of the study. Accordingly, DS kindly request to applicant to provide the available HCD in order to complete the whole assessment.
RAC's response
Thank you very much for your comments. RAC will consider all arguments in the weight of evidence during discussion in plenary sessions.

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
27.04.2022	Germany		MemberState	9
Comment received				
see attachment ECHA note – An attachment was submitted with the comment above. Refer to public attachment DE-CA_Comments_CLH-biphenyl-2-ol_2-phenylphenol_2-hydroxybiphenyl_non_conf.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment DE-CA_Comments_CLH-biphenyl-2-ol_2-phenylphenol_2-hydroxybiphenyl_final.pdf				
Dossier Submitter's Response				
DS acknowledges the comment. Thank you for the support.				
RAC's response				
Thank you very much. Noted.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
27.04.2022	Germany		MemberState	10
Comment received				
see attachment ECHA note – An attachment was submitted with the comment above. Refer to public attachment DE-CA_Comments_CLH-biphenyl-2-ol_2-phenylphenol_2-hydroxybiphenyl_non_conf.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment DE-CA_Comments_CLH-biphenyl-2-ol_2-phenylphenol_2-hydroxybiphenyl_final.pdf				

Dossier Submitter's Response
DS acknowledges the comment. Thank you for the support.
RAC's response
Thank you very much. Noted.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
27.04.2022	Germany		MemberState	11
Comment received				
see attachment ECHA note – An attachment was submitted with the comment above. Refer to public attachment DE-CA_Comments_CLH-biphenyl-2-ol_2-phenylphenol_2-hydroxybiphenyl_non_conf.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment DE-CA_Comments_CLH-biphenyl-2-ol_2-phenylphenol_2-hydroxybiphenyl_final.pdf				
Dossier Submitter's Response				
DS acknowledges the comment. The proposal to change this classification is based on the available data included in the 2021 renewal assessment report (RAR) of OPP, prepared according to Regulation (EC) No 1107/2009. It should be noted that the classification of 2-phenylphenol included in Regulation (EC) No. 1272/2008, was modified for the last time in May 2000 (by Commission Directive 2000/32/EC). In one hand, as commented, CLP guidance (2017) indicates that: *It is a reasonable assumption that corrosive substances may also cause respiratory tract irritation when inhaled at exposure concentrations below those causing frank respiratory tract corrosion. If there is evidence from animal studies or from human experience to support this then Category 3 may be appropriate.* In this regard, OPP data on humans does not provide any evidence of respiratory irritation and no clinical signs or necropsy findings reported evidence of respiratory tract irritation in animals either. Moreover, the abovementioned CLP guidance (2017) follows: *In general, a classification for corrosivity is considered to implicitly cover the potential to cause RTI and so the additional Category 3 is considered to be superfluous, although it can be assigned at the discretion of the classifier. The Category 3 classification would occur only when more severe effects in the respiratory system are not observed.* DS understands that, although irritation of the respiratory tract is expected due to the corrosiveness of the substance, the lack of evidence in the available data does not grant the classification as STOT SE 3 (H335). Regarding the comment on Vol. 3, point B.6.9.5 of the RAR, where SD mentioned that OPP and SOPP are considered irritant to the respiratory tract, the explanation is given in the abovementioned CLP Guidance: it can be assumed that the corrosive substances cause respiratory tract irritation (RTI), although it does not grant the classification as STOT SE 3 (H335). However, DS understands the referred sentence may give a sense of discrepancy.				
RAC's response				
Thank you very much for your comments. RAC will consider all arguments in the weight of evidence during discussion in plenary sessions.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
27.04.2022	Germany		MemberState	12

Comment received

see attachment

ECHA note – An attachment was submitted with the comment above. Refer to public attachment DE-CA_Comments_CLH-biphenyl-2-ol_2-phenylphenol_2-hydroxybiphenyl_non_conf.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment DE-CA_Comments_CLH-biphenyl-2-ol_2-phenylphenol_2-hydroxybiphenyl_final.pdf

Dossier Submitter's Response

As the ECHA Guidance states:

A substance is considered to be not rapidly degradable unless at least one of the following is fulfilled:

a. The substance is demonstrated to be readily biodegradable in a 28-day test for ready biodegradability. The pass level of the test (70 % DOC removal or 60 % theoretical oxygen demand) must be achieved within 10 days from the onset of biodegradation, if it is possible to evaluate this according to the available test data (the ten-day window condition may be waived for complex multi-component substances and the pass level applied at 28 days, as discussed in point II.2.3 of Annex II to this document). If this is not possible, then the pass level should be evaluated within a 14 days time window if possible, or after the end of the test; o

[…]

As it has been demonstrated to be readily biodegradable in 28-day tests, no further data is needed to assess this property.

Indeed, data of 2-phenylphenol in surface water have been given. However, these data are difficult to interpret in the context of classification purposes. These studies are mainly focused to determine the concentration of 2-phenylphenol in waste water treatment plants (WWTP) and urban sewage waters. 2-phenylphenol is widely used, as disinfectant in human medicine, as fungicide in agriculture or in household detergents or cosmetics. And so it is of no surprised the observed contamination in municipal STP discharges.

RAC's response

RAC agrees with the DS response.

PUBLIC ATTACHMENTS
1. DE-CA_Comments_CLH-biphenyl-2-ol_2-phenylphenol_2-hydroxybiphenyl_non_conf.pdf [Please refer to comment No. 2, 4, 6, 8, 9, 10, 11, 12]
2. Public Attachments_LANXESS.7z [Please refer to comment No. 1, 3, 5, 7]

CONFIDENTIAL ATTACHMENTS
1. DE-CA_Comments_CLH-biphenyl-2-ol_2-phenylphenol_2-hydroxybiphenyl_final.pdf [Please refer to comment No. 2, 4, 6, 8, 9, 10, 11, 12]2.
CONFIDENTIAL_Attachm_New_Muta_Studies_LANXESS.7z [Please refer to comment No. 1, 3, 5, 7]