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 04.09.2023

Substance name: *N*-1,3-dimethylbutyl-*N*'-phenyl-*p*-phenylenediamine
CAS number: 793-24-8
EC number: 212-344-0
Dossier submitter: Austria

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2023	France		MemberState	1
Comment received				
Aniline is a major identified hydrolysis product of the substance from a study in simulated gastric juice. This substance presents various toxicological hazards, as characterized by its harmonised classification. Do you have considered the contribution of this metabolite in the toxicity of the substance for the endpoints proposed for classification?				

Date	Country	Organisation	Type of Organisation	Comment number
29.08.2023	Germany	EU PPD Consortium (Registrants of 6PPD)	Industry or trade association	2
Comment received				
The EU PPD Consortium consisting of the Lead Registrant for 6PPD Flexsys Chemicals Belgium NV and the Consortium Members LANXESS Deutschland GmbH and Sennics Europe B.V. noted the draft CLH report and proposed harmonised classification for 6PPD and analysed the justification for proposing classification beyond the self-classification as included in the registration dossiers of the members, in particular the M-Factor for acute aquatic toxicity. In the attached document the EU PPD Consortium comments on the proposed classification and offers perspective on the specific toxicity towards coho salmon (O. kisutch). ECHA note – An attachment was submitted with the comment above. Refer to public attachment Currenta 6PPD CLH Report comment 2023-08-29.pdf				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2023	United Kingdom	<confidential>	National Authority	3
Comment received				
N-1,3-dimethylbutyl-N'-phenyl-p-phenylenediamine (6PPD)				

Hazard category: Reproductive toxicity

The dossier submitter has proposed classification with Repr. 1B (H360D). It is not clear whether the criteria for Category 1B are met, and we would welcome a fuller discussion on the following points:

• Effects are observed in the rabbit PNDT studies (anonymous 1976 and 2018) including post implantation loss/early resorptions, a reduced number of viable foetuses as well as reduced mean foetal body weights.
• We note the foetal weight decreases at doses 50 mg/kg bw/day and above in the 2018 rabbit PNDT study (8.7% and 18% at 50 and 100 mg/kg bw/day respectively), but also note that 3 does in the high dose in this treatment group had marked body weight decreases and abortions. Could foetuses from these 3 does have confounded interpretation of the very severe foetal body weight decreases noted at the top dose?
• The 1976 rabbit PNDT study has numerous methodological deficiencies which limit its use in informing on any potential adverse effects on development.
• Effects are observed in rat studies (PNDT, screening study, three generation study, EOGRTS) including increased number of resorptions, reduced number of live pups, impairment of pup survival, lower foetal body weight from 10 mg/kg bw/day. It is quite likely that the decreases in live pups and poor perinatal survival noted in the EOGRTS are a direct consequence of the prolonged parturition reported in this study. Therefore there is a degree of uncertainty surrounding the interpretation of these findings.
• No treatment-related malformations were reported in the rat and rabbit standard developmental toxicity studies.
• Effects seen in the pubertal assays in rats including delayed VO, changes to reproductive tissue weights, and histological changes suggesting irregular oestrus cyclicity might indicate possible test substance-related endocrine-mediated effects. However, as these were accompanied by significantly decreases in body weights, it is unclear if these effects are direct effects of treatment or secondary to stress associated with general systemic toxicity.

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2023	France		MemberState	4

Comment received

Fertility:

The recent EOGRTS reports a clear effect on female fertility as characterised by dystocia seen at doses equal and above 20 mg/kg bw/d.

The previous range finding study reports similar effect, even if it can be noted that dystocia generally occurred at the dose of 100 mg/kg bw/d in females presenting an important body weight loss. It is not clear if the decreased body weight relates to dead foetuses or to a direct toxicity on dams. Gestation length was increased at 50 and 100 mg/kg bw/d and can be linked to the observed dystocia.

In the OECD 421 study, even if no dystocia was reported, the duration of gestation was significantly increased at the dose of 100 mg/kg bw/d.

No reproductive effect was noted in the 3-generation study presenting various limitations. In addition, administration was performed in the diet that may also explain the different profile of toxicity compared to the EOGRTS and range finding study.

No effect on reproduction organs was noted in the chronic study. This is not inconsistent with the other studies cited in this section since histopathological findings was neither identified in reproductive organs. Moreover, this study is not designed to investigate effects on fertility function.

In the OECD 421 study, only an increased trend of gestation length was reported (with 5 females having pregnancy > 23 days compared to 2 in the control group). This study was performed at doses lower than those used in the EOGRTS and range finding study but points to similar effect on female reproduction.

Overall, consistent effects on female reproductive function (dystocia and increased gestation length) are reported in different studies in the absence of excessive general toxicity. This justifies a classification as Repr. 1B for fertility.

Development:

In the OECD 414 study in rat, there is no developmental effect that can justify a classification according to CLP Regulation.

Abortions and post-implantation losses are reported in the OECD 414 study in rabbits (Anonymous, 2018c). From table 51, it is not clear if the body weight loss is attributed to the dead foetuses or to a general maternal toxicity. Could you please clarify?
Regarding post-implantation loss, the fact that difference was not statistically significant can be explained by the large standard deviation in the 100 mg/kg bw/d group. Do you have access to individual data in order to further investigate this point?
Concerning malformations, it is noted in table 55 that 11 foetuses presented polydactyly in the 25 mg/kg bw/d group. Could you please provide more information on this point or is it a mistake in the number?

In the OECD 421 study (Tanaka, 2001), the number of total live pups born was reduced. However, this occurs in a context of increased gestation length. Thus, from this study, it is not clear if the reduction of total live born is a direct developmental toxicity effect or secondary to effect on female fertility function.

Impairment of pup survival during lactation occurs in the OECD 443 study and in its range finding study.

Overall, lethality of offspring is consistently reported in different studies using different protocols.

Pubertal studies also point to developmental toxicity that raise concern for endocrine disruption in offspring (e.g. effects on thyroid, ovaries, uterus, oestrous cycle, vaginal opening, balanopreputial separation…).

Based on these effects, FR agrees with the proposed classification as Rep. 1B for development.

Effects on or via lactation:
There is no study investigating solely effects on lactation.

The OECD 443 study and its range finding study report developmental effects during lactation (primarily decreased survival and body weight). However, taken into account the study designs, it cannot be distinguish if these effects are due to in utero exposure and/or

exposure during lactation.

Nevertheless, it cannot be noted that more pups present absence of milk in their stomach in the highest tested dose compared to the control group. Furthermore, dosage of milk shows that the substance is present in the milk of dams (content increasing with the dose).

In summary, the data do not allow classifying the substance for effects on or via lactation.

Date	Country	Organisation	Type of Organisation	Comment number
23.08.2023	Germany		MemberState	5
Comment received				
Classification for fertility is supported based on dystocia/prolonged labour/adverse clinical signs during parturition/increased gestation length in EOGRT- and screening studies. Classification for development is supported based on reduced pre- and postnatal survival and lower foetal/pup body weights linked to adverse outcome later in life.				

Date	Country	Organisation	Type of Organisation	Comment number
29.08.2023	Germany	EU PPD Consortium (Registrants of 6PPD)	Industry or trade association	6
Comment received				
Please refer to the attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Currenta 6PPD CLH Report comment 2023-08-29.pdf				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
23.08.2023	Germany		MemberState	7
Comment received				
The classification proposal is supported because of guideline-conform acute toxicity data placing the substance in the corresponding range.				

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2023	France		MemberState	8
Comment received				
FR agrees with the proposed classification as Acute Tox 4 and associated ATE of 890 mg/kg bw based on the lowest LD50.				

Date	Country	Organisation	Type of Organisation	Comment number
29.08.2023	Germany	EU PPD Consortium (Registrants of 6PPD)	Industry or trade association	9
Comment received				

Please refer to the attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Currenta 6PPD CLH Report comment 2023-08-29.pdf

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
23.08.2023	Germany		MemberState	10
Comment received				
Classification is supported based on the presented human and animal data.				

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2023	France		MemberState	11
Comment received				
FR agrees with the classification proposal Skin Sens. 1A as the animals and human studies show sensitization reactions. Regarding the study of Yamano et al. (2009), an estimated EC3 is proposed. However, according to CLP guidance, 2017, there is no guidance for subcategorisation for studies conducted according to OECD TG 442B or equivalent protocols. The estimation of an EC3 is therefore not relevant for comparison to CLP criteria and can be removed. We agree with the subcategorization 1A but we think that more details could be added in the justification since different results / potencies are obtained from the existing data (what test(s) considered as key study for subcategorization using CLP criteria set in Tables 3.6 and 3.7). Regarding human studies, we understand that these studies are difficult to assess due to cross-sensitization reactions as well as poor reporting. Could you please compare the results of these studies with CLP criteria set in tables 3.2, 3.3 and 3.4 of the CLP guidance?				

Date	Country	Organisation	Type of Organisation	Comment number
29.08.2023	Germany	EU PPD Consortium (Registrants of 6PPD)	Industry or trade association	12
Comment received				
Please refer to the attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Currenta 6PPD CLH Report comment 2023-08-29.pdf				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2023	France		MemberState	13
Comment received				
Not all existing repeated dose toxicity studies are considered in this endpoint. Could you please explain why others studies (e.g. pubertal assays with about 20 days of exposure) are not included in this section?				

Consistent effects are reported among the available studies, consisting mainly in toxicity in the liver and in blood system.

FR considers that significant toxicity is observed in the liver, characterized in particular by necrosis and vacuolar degeneration. Moreover, this is associated with an increase of liver weight (generally higher than 10%) and modifications of biochemical parameters. This is not considered as adaptive responses.

Concerning blood system, more details would be helpful to conclude if anemia should be considered as significant toxicity according to CLP criteria.

These effects occurred at doses compatible with the ranges leading to a classification as STOT RE (mainly category 2).

Date	Country	Organisation	Type of Organisation	Comment number
29.08.2023	Germany	EU PPD Consortium (Registrants of 6PPD)	Industry or trade association	14

Comment received

Please refer to the attached document.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Currenta 6PPD CLH Report comment 2023-08-29.pdf

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
31.08.2023	France		MemberState	15

Comment received

FR agrees that 6PPD can be considered not readily biodegradable based on the results of the OECD 301C (1994) and the degradation products.

Acute aquatic hazard: FR agrees with the classification proposal Aquatic Acute 1 and the M-Factor of 10000 using the lowest acute toxicity value of 6PPD and its degradation products. We agree with the approach of using the degradation product 6PPD-quinone which is more toxic than the parent substance to establish the M-Factor as the CLP guidance (2017) indicates (p 507) "Normally, the identification of hazard, and hence the classification will be based on information directly obtained from testing of the substance being considered. There are occasions, however, where this can create difficulties or the outcomes do not conform to common sense. For example, some chemicals, although stable in the bottle, will react rapidly (or slowly) in water giving rise to degradation products that may have different properties. Where such degradation is rapid, the available test data will frequently define the hazard of the degradation products since it will be these that have been tested. These data may be used to classify the parent substance in the normal way".

Chronic aquatic hazard: FR agrees with the classification proposal Aquatic Chronic 1 and the M-Factor of 10 using the lowest chronic toxicity value of 6PPD and its degradation products.

Date	Country	Organisation	Type of Organisation	Comment number

29.08.2023	United Kingdom	Health and Safety Executive	National Authority	16
Comment received				
N-1,3-dimethylbutyl-N'-phenyl-p-phenylenediamine (EC: 212-344-0; CAS: 793-24-8) Noting the DS considers 6PPD-quinone (6PPDQ) a relevant degradant for hazard classification, we agree literature data for 6PPDQ should be assessed. The CLH report includes the Tian et al. studies (2021 and 2022) which the DS considers relevant and reliable (K2) for hazard classification. The lowest endpoint is a 24-hour LC50 of 0.00007928 mg/L (based on DS recalculation and measured concentrations) for O. kisutch. While toxicity data for O. kisutch are lower than those for similar fish species, we agree these more sensitive species-specific endpoints are relevant for hazard classification. Interestingly recent research (Montgomery et al., 2023 preprint) considers such different sensitivities in relation to differences in biotransformation enzymes across species. We recognise the timescales for CLH report preparation and highlight the below publication which has recently been published: Lo, B.P., Marlatt, V.L., Liao, X., Reger, S., Gallilee, C., Ross, A.R.S. and Brown, T.M. (2023), Acute Toxicity of 6PPD-Quinone to Early Life Stage Juvenile Chinook (Oncorhynchus tshawytscha) and Coho (Oncorhynchus kisutch) Salmon. Environ Toxicol Chem, 42: 815-822. https://doi.org/10.1002/etc.5568 The Lo et al., 2023 study test design is similar to Tian et al., 2022 and broadly follows an Environment Canada method comparable to OECD TG203. The dose-response for O. kisutch is presented using ~3 week old juvenile fish and additional information is available in the supplementary information with a note that raw data are available on request. The study reports a 24-hour LC50 of 0.000041 mg/L based on initial measured concentrations. Given measured data indicate >20% losses over the exposure duration, it appears mean measured endpoints would be preferable and likely more conservative. Please can the DS consider this study and the application of this endpoint which although in the same hazard classification range as Tian et al., 2022 is more sensitive. Given the absence of chronic toxicity data for O. kisutch and the sensitivity of this species in acute toxicity tests, the use of the surrogate approach with these acute data should be considered for the aquatic chronic classification. David Montgomery, Xiaowen Ji, Jenna Cantin, Danielle Philibert, Garrett Foster, Summer Selinger, Niteesh Jain, Justin Miller, Jenifer McIntyre, Benjamin de Jourdan, Steve Wiseman, Markus Hecker, Markus Brinkmann (2023 preprint), Toxicokinetic Characterization of the Inter-Species Differences in 6PPD-Quinone Toxicity Across Seven Fish Species: Metabolite Identification and Semi-Quantification. bioRxiv 2023.08.18.553920; doi: https://doi.org/10.1101/2023.08.18.553920				

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2023	Belgium		MemberState	17
Comment received				
We support the proposed classification and M-factors: Aquatic acute 1, H400, Macute = 10 000 Aquatic Chronic 1, H410, Mchronic = 10 For 6PPD, reliable acute aquatic toxicity data are available for fish and invertebrates (fish Oryzias latipes LC50= 0.028 mg/L, invertebrate Daphnia magna EC50= 0.023 mg/L)				

leading to a classification of Acute aquatic toxicity 1, H400.
6PDD is not readily biodegradable but hydrolyses quickly (half-life <16 days). However, degradation products fulfil the criteria for classification as hazardous to the aquatic environment and therefore the parent compound is considered not rapidly degradable. Nevertheless, we agree with the dossier submitter that toxicity can be attributed to the degradation products (hydrolysis, photodegradation and oxidation/ozonation), and more specific to 6PPD-quinone which has the lowest acute toxicity value (fish LC50 = 0.000079 mg/L) of the tested degradation products. Therefore, we agree that an M-factor of 10 000 is warranted.

For 6PPD, only a reliable chronic toxicity study is available for fish (Oryzias latipes) resulting in a NOEC of 0.0037 mg/L, leading to a classification of Aquatic Chronic 1, H4100 and M factor of 10. Applying the surrogate approach, 6-PPD warrants also a classification as Aquatic Chronic 1, H410 and M factor of 10, based on the EC50 invertebrates (Daphnia magna) of 0.023 mg/L.
Degradation products of 6PPD have a similar or lower chronic toxicity than the parent compound. Therefore we agree with an M-factor chronic of 10.

Date	Country	Organisation	Type of Organisation	Comment number
29.08.2023	Germany	EU PPD Consortium (Registrants of 6PPD)	Industry or trade association	18
Comment received				
Please refer to the attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Currenta 6PPD CLH Report comment 2023-08-29.pdf				

PUBLIC ATTACHMENTS
1. Currenta 6PPD CLH Report comment 2023-08-29.pdf [Please refer to comment No. 2, 6, 9, 12, 14, 18]