

Public comments on CLH proposal for Perfluoroheptanoic acid (EC 206-798-9, CAS 375-85-9), submitted by Belgian Federal Public Service Health, Food Chain Safety and Environment Risk Management service (Dossier submitter).

Reference: CLH report available on ECHA website at <https://echa.europa.eu/documents/10162/c9c9b080-2704-3052-08a8-e1bb7964b1b8>, retrieved on 21 January 2020

By way of background, the Belgian Competent Authority has submitted to the European Chemicals Agency (“the Agency”) a proposal for harmonised classification and labelling of perfluoroheptanoic acid; tridecafluoroheptanoic acid (“PFHpA” or “the Substance”)¹ dated October 2019 (“the CLH Proposal”) under Regulation (EC) 1272/2008 (“the CLP Regulation”).² Thereby, “[b]ased on the results of the Combined 90-Day Repeated Dose Oral (Gavage) Toxicity Study with the Reproduction/Developmental Toxicity Screening Test with sodium perfluoroheptanoate (EC 243-518-4)”, PFHpA is proposed to be classified as toxic for reproduction, category 1B (Repro. 1B), and Specific Target Organ Toxicity- Repeated Exposure, category 1 (STOT RE 1).³ PFHpA is “a common potential degradation product of all substances that contain a perfluorinated linear chain of six carbon atoms connected by a terminal perfluorinated carbon atom to another non-fluorinated carbon atom”.⁴ The Substance is a degradation product of a registered substance.

The Substance is neither registered under Regulation 1907/2006 (“the REACH Regulation”)⁵ nor listed in Annex VI to the CLP Regulation.⁶

In this document, we provide comments to two separate aspects of the CLH proposal:

- i. General comments on the scope and applicability of this CLH proposal
- ii. Specific comments on the proposed hazard class of reproductive toxicity

¹ EC 206-798-9; CAS 375-85-9.

² Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (*OJ L 353, 31.12.2008*, p. 1).

³ Page 10 of the CLH Proposal.

⁴ Page 10 of the CLH Proposal.

⁵ Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (*OJ L 396, 30.12.2006*, p. 1).

⁶ Page 5 and 9-10 of the CLH Proposal. Self-classifications exist in the Classification & Labelling inventory as Acute Tox. 4, Skin Corr. 1B, Met. Corr. 1, Eye Dam. 1.

i. General comments on the scope and applicability of a CLH proposal for a degradation product

The scope and purpose of the CLP Regulation is stated in its Article 1. In summary, the CLP Regulation aims “*to ensure a high level of protection of human health and the environment as well as the free movement of substances, mixtures and articles*”. It does so by establishing a system based on harmonised criteria for the classification and labelling of substances and mixtures.

The CLP Regulation imposes an **obligation** for manufacturers, importers and downstream users to classify substances and mixtures **placed on the market** (Article 1(b)(i) of the CLP Regulation). Accordingly, Article 4(1) of the CLP Regulation requires “*manufacturers, importers and downstream users shall classify substances or mixtures in accordance with Title II before placing them on the market*” (emphasis added).

Per Article 4(1) of the CLP Regulation, **the general obligation to classify is imposed only before a substance/mixture is placed on the market**. Placing the substance/mixture on the market is, therefore, necessary for a substance/mixture to be subject to the classification obligation.

This reading is confirmed by the provision of a specific requirement for manufacturers, producers of articles and importers to classify certain substances which are not placed on the market – *i.e.* those subject to registration or notification under Regulation (EC) No 1907/2006,⁷ and more specifically:

- a. substances must be registered under Articles 6, 7(1) or (5), 17 or 18 of the REACH Regulation;
- b. substances must be notified under Articles 7(2) or 9 of the REACH Regulation.⁸

Therefore, the classification of substances which are not placed on the market must be considered an exception to the general obligation to classify which applies (instead) to substances which are to be placed on the market. Substances which are not to be placed on the market are subject to the classification obligation only where so is expressly provided.

The structure of the harmonised classification dossier as prescribed by law also supports that a substance cannot be subject to harmonised classification unless it is placed on the

⁷ Articles 1(1)(b) of the CLP Regulation.

⁸ We understand that PFHpA is neither subject to notification under Articles 7(2) or 9 of the REACH Regulation, nor is subject to registration under Articles 6, 7(1) or (5), 17 or 18 thereof.

market or, although it is not placed on the market, unless it falls under the scope of Article 4(2) of the CLP Regulation.

Under Article 37(1) of the CLP Regulation, “[a] competent authority may submit to the Agency a proposal for harmonised classification and labelling of substances [...]. The proposal shall follow the format set out in Part 2 of Annex VI and contain the relevant information provided for in Part 1 of Annex VI.” In turn, Part 2 of Annex VI to the CLP Regulation provides that “[a] comparison of the available information with the criteria contained in Parts 2 to 5 [...] shall be completed and documented in the format set out in Part B of the Chemical Safety Report in Annex I to Regulation (EC) No 1907/2006.”

That format of the Chemical Safety Report does not appear fit for degradation products, in that it requires, amongst others, information on:

- “Manufacture and uses” (Section 2): this information cannot be part of the CLH Proposal in so far as PFHpA is neither manufactured nor used as such. Instead, it is “a common potential degradation product” of perfluorinated substances;
- “Degradation” (Section 4.1): PFHpA is a metabolite of a registered substance only formed from biodegradation of substances such as Ammonium salts of mono- and bis[3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl and/or poly (substituted alkene)] phosphate when released into the environment.⁹ Section 4.1 of the Chemical Safety Report is dedicated to information concerning the degradation of a substance, including its degradation products.

It follows from the above that the hazards intrinsic to the degradation product of a substance can be assessed as part of the hazard classification of that substance. This classification “is principally concerned with the aquatic environment and the basis of the identification of hazard is the aquatic toxicity of the substance or mixture, and information on the degradation and bioaccumulation behaviour.”¹⁰ This is further supported, amongst others, by Section 4.1.1.3.1¹¹ and Section 4.1.2.9.3¹² of Annex I to the CLP Regulation.

⁹ Comments of 1 February 2019 submitted by Chemours Netherlands B.V. on the draft decision SEV-D-2114454199-40-01/D on substance evaluation of Ammonium salts of mono- and bis[3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl and/or poly (substituted alkene)] phosphate .

¹⁰ ECHA Guidance on the Application of the CLP Criteria, version 5.0 – July 2017, page 57.

¹¹ Section 4.1.1.3.1 of Annex I to the CLP Regulation provides that “[c]lassification of substances and mixtures for environmental hazards requires the identification of the hazards they present to the aquatic environment. [...] The basis, therefore, of the identification of hazard is the aquatic toxicity of the substance or mixture, although this shall be modified by taking account of further information on the degradation and bioaccumulation behaviour, if appropriate.”

¹² Section 4.1.2.9.3 of Annex I to the CLP Regulation provides that “[m]any degradation data are available in the form of degradation half-lives and these can be used in defining rapid degradation provided that ultimate biodegradation of the substance [...] is achieved. Primary biodegradation does not normally suffice in the assessment of rapid degradability unless it can be demonstrated that the degradation products do not fulfil the criteria for classification as hazardous to the aquatic environment.”

Article 37 of the CLP Regulation entitles the Committee for Risk Assessment of the Agency (“RAC”) to adopt an opinion on a proposal for harmonised classification submitted by the Competent Authority of a Member State.

The competence of the RAC extends only so far as the substance can be subject to harmonised classification under the CLP Regulation. As illustrated above, a substance cannot be subject to harmonised classification unless it is placed on the market or it falls under the scope of Article 4(2) of the CLP Regulation.

Since the Substance is not placed on the market and it is not in one of the situations described by Article 4(2) of the CLP Regulation, the RAC has no competence to adopt an opinion on the degradation product PFHpA.

In *summary*, only substances that are placed on the market in the EU, or substances in the scope of Article 4(2) of the CLP Regulation, can be subject to the harmonized classification procedure. Accordingly, RAC does not have the competence to issue an opinion on the proposal to classify the Substance, since the Substance is not placed on the market in the EU.

ii Specific comments on the proposed hazard class of reproductive toxicity

We strongly disagree with the proposed reproductive toxicity classification in the CLH Proposal as it lacks scientific justification. The proposal relies on one single study in mice, which is detailed in the annex to the proposal and referenced as “Combined 90-day repeated dose toxicity study with reproduction/developmental toxicity screening (anonymous, 2017). “As described below, the proposed classification contradicts the study results.

The decreased post-natal survival, decreased pup body weights, and vaginal patency are secondary to the overt maternal toxicity observed at the 50 mg/kg bw/day high dose. The maternal toxicity was considered potent enough to justify a STOT RE liver target organ, so it cannot be claimed, as stated in the CLH Proposal, that findings in the pups occurred with an “absence of marked maternal toxicity”. The definition of maternal toxicity is not limited to only pup toxicity occurring through a lack of maternal care; the health of the dams must be considered. Further, the observation of cleft palate is within the range of occurrence-by-chance in the historical control and lacks a dose response, therefore it cannot be attributed to the test substance. Therefore, the findings described in the CLH Proposal do not justify classification for the reproductive toxicity endpoint.

As noted in CLH Proposal Section 10.10.6, vaginal patency, post-natal survival, and pup body weights were decreased at the highest dose level of 50 mg/kg bw/day in the Study. In that same section of the Proposal, the effects observed in the pups are stated to occur “in the absence of marked maternal toxicity”. The CLH Proposal justifies this

statement by limiting the definition of “maternal toxicity” to “adverse effects in pups that occur as a result of a reduction of maternal care.” This is a special case – *i.e.*, lack of maternal care – and is most certainly not the *only* mechanism by which maternal health can influence offspring. The Category 1B definition (provided in Section 10.10.6) is more consistent with the standard definition of how maternal toxicity must be considered in light of effects in pups:

“Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be secondary non-specific consequence of other toxic effects.”

At the 50 mg/kg bw/day high dose, there was clear evidence of maternal toxicity as indicated by the changes in maternal blood chemistry, specifically ALP and triglycerides, observed in lactating females at the 50 mg/kg bw/d high dose (Proposal Table 11). CLH Proposal Section 10.12.1 states that the liver toxicity observed in the Study was significant enough to propose classification as a STOT RE with liver as a target organ. Section 10.12.2 of the Proposal states that “test substance related effects on the liver were seen in this study starting at doses as low as 0.5 mg/kg bw/d”, there were “...significant alteration of liver function”, “...severe effects...”, and that “significant adverse effects on the liver were thus observed after exposure...” and “...effects seen in the liver appeared already significant at 8.3 mg/kg bw/d”. Based on the liver toxicity description in Section 10.12.2 of the Proposal, the Dossier Submitter acknowledges that there are significant adverse effects on the maternal generation. Therefore, it is not surprising to observe secondary effects in the pups at the 50 mg/kg bw/d high dose. The effects observed in the pups must be viewed as secondary to the overt maternal toxicity observed in the dams at the 50 mg/kg/day dose. This means that these findings do not support a Reproductive Toxicity classification. Also, it must be noted that the CA is reinterpreting results of a Study and deriving conclusions that contradict the study authors. The delayed vaginal patency was discussed in the Study report and the Study Director and subject matter experts state explicitly that “this delay was considered secondary to the lower mean body weights observed in this group”. Since delayed vaginal patency is secondary, it cannot be used to justify a Reproductive Toxicity classification.

Further, in the Study, cleft palate was observed in 6 pups from 1 litter at the lowest dose (0.5 mg/kg/day) and in 3 pups from 2 litters in the high dose (50 mg/kg/day). Importantly, no incidents of cleft palate were observed in the mid dose (10 mg/kg/day). The Proposal authors state that they “... [do] not consider this effect as a chance finding”. This is an opinion unsupported by fact. The weight that the CLH Proposal places on cleft palate directly contradicts the conclusion of the Study Director of that Study. The observation of cleft palate was specifically addressed in the Study report:

The malformation of cleft palate (entire length) [was] noted for 6(1) and 3(2) pups (litters) in the 0.5 and 50 mg/kg/day groups, respectively. Because this finding did not occur in a dose related manner, it was not considered test substance related.

The Study report authors, who are subject matter experts in this field, did not consider the cleft palate finding to be test substance related. Similarly to the example of vaginal patency discussed above, no scientific explanation was presented as to why the Proposal authors dismissed the scientific conclusions of the Study Director and the subject matter experts who performed the Study. The Proposal describes cleft palate as “a rare malformation” but in this strain of mice the incidence is approximately 10% litter basis or 2% fetus basis (CRL, 2019). The study required a large number of mice. It is unsurprising that cleft palate was observed by chance. A simple statistical analysis shows that with approximately 75 litters and a 12% litter basis for cleft palate by chance alone, one could expect about 9 litters to be affected. In addition, the historical control data¹³ (CRL, 2019) indicates an observed incidence of cleft palate in 2% of fetuses. Therefore, one could expect approximately 16 instances of cleft palate for a study of this size by chance alone (2%/100 x 800 fetuses). There are only 9 instances of fetuses with cleft palate in this study and chance alone could be expected to produce 16. Therefore, the cleft palate observation is expected and can be attributed to chance alone and cannot plausibly be attributed to the test substance.

Furthermore, the lack of a dose response associated with cleft palate also indicates that this finding is not related to the test substance. A dose 20 times greater than the low dose did not induce cleft palate, and a dose of 100 times higher than the low dose showed a decrease in cleft palate (fetus basis) relative to the low dose. There was no dose response; this finding was not the result of test substance exposure.

In summary, the decreased post-natal survival, decreased pup body weights, and vaginal patency are secondary to the overt maternal toxicity observed at the 50 mg/kg bw/day high dose. The maternal toxicity was considered potent enough to justify a STOT RE liver target organ, so it cannot be claimed, as stated in the CLH Proposal, that findings in the pups occurred with an “absence of marked maternal toxicity”. The definition of maternal toxicity is not limited to only pup toxicity occurring through a lack of maternal care; the health of the dams must be considered. Further, the observation of cleft palate is within the range of occurrence-by-chance in the historical control and lacks a dose response, therefore it cannot be attributed to the test substance. Therefore, the findings described in the CHL Proposal do not justify classification for the reproductive toxicity endpoint.

¹³ CRL, 2019. Mouse Historical Control Data is publicly available here: <https://www.criver.com/sites/default/files/noindex/historical-control-data/hcd-pa-mice.pdf>