Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Nonadecafluorodecanoic acid (PFDA) [1] and its ammonium (PFD-A) [2] and sodium (PFD-S) [3] salts

Nonadecafluorodecanoic acid [1], ammonium nonadecafluorodecanoate [2], sodium nonadecafluorodecanoate [3]

EC Numbers: 206-400-3 [1], 221-470-5 [2], - [3]
CAS Numbers: 335-76-2 [1], 3108-42-7 [2], 3830-45-3 [3]

CLH-O-0000001412-86-92/F

Adopted
4 December 2015

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON NONADECAFLUORODECANOIC ACID; AMMONIUM NONADECAFLUORODECANOATE; SODIUM NONADECAFLUORODECANOATE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Chemicals name: Nonadecafluorodecanoic acid (PFDA) [1] and its ammonium (PFD-A) [2] and sodium (PFD-S) [3] salts
EC numbers: 206-400-3 [1], 221-470-5 [2], - [3]
CAS numbers: 335-76-2 [1], 3108-42-7 [2], 3830-45-3 [3]

Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
10.07.2015	Denmark		MemberState	1
Comment received				
The Danish CA supports the proposed classifications of PFDA for reproductive toxicity including lactation (Repr. 1B; H360 Df and Lact.; H362) and carcinogenicity (Carc. 2; H351) based on read-across PFOA and APFO. As supporting evidence we would furthermore like to highlight a recent Danish study on the "Association between Perfluorinated Compound Exposure and Miscarriage in Danish Pregnant Women" (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4388566/). The study is based pregnant women participating in a child cohort and has shown, that women with spontaneous miscarriages had higher levels of PFNA and PFDA than women giving birth. Those women with the highest exposures to PFDA and PFNA had an increased risk (by a factor 16) of miscarriage.				
Dossier Submitter's Response				
Thank you for your support. We note the Danish study (case-control study within a population-based, prospective cohort) that adds support to identifying PFDA (as well as PFNA) as a reproductive toxicant.				
RAC's response				
The support is noted.				

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	France		MemberState	2
Comment received				
Toxicokinetic – Human studies				

Additional human data on PFDA have not been included in the report:

Mean levels of PFDA (0.53 ng/mL) in the sera of women in Sweden were lower than levels of PFOS (20.7 ng/mL), PFHxS (4.7 ng/mL), PFOA (3.8 ng/mL) and PFNA (0.80 ng/mL), but higher than those of PFUnDA (0.40 ng/mL) and FOSA (90.24 ng/mL). PFDA was not detected in any of the human milk samples tested (LOD 0.008 ng/mL) (Karrman et al., 2007, Kim et al., 2011).

Karrman et al. (2007) measured the levels of PFOA, PFNA, PFDA, PFUnDA, PFHxS, PFOS and FOSA in milk and maternal serum taken from primiparous Swedish women. Similarly, Kim et al. (2011c) measured the levels of PFASs in maternal serum, umbilical cord serum, and breast milk taken from the general population of Seoul, South Korea. They showed that levels of PFOA (3.8 ng/mL) in serum were lower than PFOS (20.7 ng/mL) and PFHxS (4.7 mL), but higher than PFNA (0.80 ng/mL), PFDA (0.53 ng/mL), PFUnDA (0.40 ng/mL) and FOSA (0.24 ng/mL) (Karrman et al., 2007), or in some cases PFOA (1.6 ng/mL) was the most predominant compound after PFOS (5.6 ng/mL) (Kim et al., 2011).
Karrman A, Ericson I, van Bavel B, Darnerud PO, Aune M, Glynn A, Lignell S and Lindstrom G, 2007. Exposure of perfluorinated chemicals through lactation: levels of matched human milk and serum and a temporal trend, 1996-2004, in Sweden. Environmental health perspectives, 115, 226-230.

Kim et al. (2011) measured the levels of PFBS, PFHxS, PFOS, PFDS, FOSA, PFHpA, PFOA, PFNA, PFDA, PFUnDA and PFDoDA in paired samples of maternal serum, umbilical cord serum, and breast milk taken from the general population of Seoul, South Korea. PFHpA was not detected in maternal sera (n = 20), cord sera (n = 20) or human milk (n = 17).The limit of detection (LOD) was < 0.26 ng/mL, < 0.13 ng/mL and < 4.45 pg/mL for maternal sera, cord sera or human milk, respectively (Kim et al., 2011c).
Kim SK, Lee KT, Kang CS, Tao L, Kannan K, Kim KR, Kim CK, Lee JS, Park PS, Yoo YW, Ha JY, Shin YS and Lee JH, 2011. Distribution of perfluorochemicals between sera and milk from the same mothers and implications for prenatal and postnatal exposures. Environmental Pollution, 159, 169-174.

The detoxification of PFASs (PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFHxS and PFOS) was investigated in a 51-year-old asymptomatic male Canadian subject. PFOA was readily excreted in the urine, but under normal conditions was not excreted in the faeces. After treatment with cholestyramine (a bile-acid sequestrant), PFOA was detected in the subject‘s faecal samples, although to a lesser extent than were PFHxS and PFOS (Genuis et al., 2010). Under normal conditions, PFDA was not detected in the subject‘s urine or faeces samples. PFNA was also not detected but after treatment with cholestyramine (a bile-acid sequestrant), PFNA was detected in his faecal samples, although to a lesser extent than were PFHxS, PFOS and PFOA (Genuis et al., 2010).
Genuis SJ, Birkholz D, Ralitsch M and Thibault N, 2010. Human detoxification of perfluorinated compounds. Public health, 124, 367-375.

It might be useful to include these date and to discuss how they may support the read across approach between PFDA and PFOA/PFNA.

Editorial comment:
Page 12 table 9 it is written that plasma half-life of PFDA is 339.92 but in the original paper it is 39.9 days in males (Ohmori, 2003).

Other toxicological endpoints:

Since APFAP/PFOA and PFNA are also classified as Acute Tox 4 – H302/332; Eye Dam 1 – H318 and STOT RE 1 H372, extrapolation of these classifications for PFDA could also have been discussed in this CLH report. Furthermore, please note that the proposed Lact. H362 is lacking in table 10.

Dossier Submitter's Response

Additional studies

Thank you for bringing attention to additional human studies on the distribution of PFDA in serum and breast milk. They will complement the current refrence list in the background document.

We agree that the studies could have been included and discussed in the dossier to support the read-across approach between PFDA and APFO/PFOA.

Kim et al., 2011 measured the levels of PFBS, PFHxS, PFOS, PFDS, FOSA, PFHpA, PFOA, PFNA, PFDA, PFUnDA and PFDoDA in paired samples of maternal serum, umbilical cord serum, and breast milk in a small sample (n=20) taken from mothers and newborn babies in South Korea. We note that in this study, PFDA was in addition to maternal serum also detected in umbilical cord serum (0.36 ng/ml in maternal serum and 0.12 ng/ml in umbilical cord serum) and a statistically significant correlation between concentrations in maternal serum and cord serum was found for PFOA, PFNA and PFDA. PFDA and PFNA were not detected above LOQ in breast milk. PFOA was detected at 1.6 ng/ml, 1.1 ng/ml and 41 pg/ml in maternal serum, umbilical cord serum and breast milk respectively.

Kärrman et al., 2007 measured the levels of PFOA, PFNA, PFDA, PFUnDA, PFHxS, PFOS and PFOSA in breast milk and maternal serum taken from primiparous Swedish women. In this study, the level of PFDA in serum samples was determined at 0.53 ng/ml (mean value), and levels of PFNA and PFOA were 0.80 and 3.8 ng/ml respectively. However, PFDA was not detected in any of the human breast milk samples tested (LOD 8 pg/mL). PFNA (2/12 sample above LOD) and PFOA (1/12 samples above LOD; blank level was >50% of the detected concentrations in eleven samples) were also determined at very low levels.

We note that PFDA was not detected in breast milk in the studies by Kim et al 2011 and Kärrman et al 2007 in contrast to the Fujii study (2012) that was included in the current dossier where PFDA was detected in the range <15-65 pg/ml. In addition, in the studies by So et al 2006 and Liu et al 2010 (referenced in the Fujii study) PFDA was found in breast milk at 7.2 pg/ml and 9.9 pg/ml. It seems that samples of breast milk from specific regions in Japan and China have higher levels of PFDA than breast milk from Sweden (Kärrman et al 2007), South Korea (Kim et al 2011) or Spain (Llorca et al., 2010; cited in the dossier). The information on the levels of PFDA in the corresponding maternal serum in the studies by Fujii et al 2012, Llorca et al 2010, So et al 2006 and Liu et al 2010 is not available to us.

The study by Genius et al., 2010 is interesting but the findings very preliminary due to the design of the study and only one subject included.

Editiorial comments

Thank you for the editorial comments. We agree to the suggested changes.

Other toxicological endpoints

Thank you for your comments, we will consider them further. We agree that since APFO/PFOA and PFNA are also classified as Acute Tox 4 – H302/332; Eye Dam 1 – H318 and STOT RE 1 - H372, extrapolation of these classifications for PFDA could also have been explored in this CLH report. However, in the current CLH report, classification in Acute Tox,

Eye Dam and STOT RE was not considered and thus these hazard classes were not opened for comments during public consultation. Therefore the current report can not be updated at this stage.

RAC's response

The RAC, after reviewing these additional studies, acknowledged that, from the extensive literature of perfluorinated compounds, some studies can provide further support while others could not reach sufficient sample size to conclude (or provided negative associations), but also considered that the DS's analysis is thorough and carefully developed, paying attention to providing a global clear picture of the data (including both studies that provided evidence that PFDA was found in breast milk and studies where it was not found) and therefore that the CLH report contained an appropriate dataset.

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2015	Germany		MemberState	3

Comment received

The dossier relies on a read-across to PFOA and other perfluorinated compounds. The read-across is carefully developed and well founded. The German CA supports the CLH-dossier and the classification as Repr. 1B (H360Df), Lact. (H362) and Carc. 2 (H351).

It is recommended that the read across considerations should also include STOT RE 1 as this endpoint was not addressed by the self classification.

In the field "related CAS information" of the reference substance in IUCLID sections 1.1 and 1.2 the CAS number for the sodium salt is wrong and should be altered to the CAS-number 3830-45-3.

Dossier Submitter's Response

Thank you for your support.

We note the German CAs recommendation to include STOT RE 1 classification. Please see our response above to comment number 2.

Thank you for making us aware of the mistake regarding CAS-number of the sodium salt in IUCLID. We agree to the change.

RAC's response

The support is noted.
The RAC has assessed the hazard classes for which data were provided in the CLH report and which were open for comments during the public consultation.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2015	Germany		MemberState	4

Comment received

The dossier relies on read-across to PFOA, only two studies using PFDA were mentioned. Both studies investigated the potential of PFDA to promote tumorigenesis, one study in rats, one in rainbow trout.

Dossier Submitter's Response
Thank you for your comment. We note the German CA support in comment number 3 and agrees with their observation that the classification in Carc. 2 relies on read-across to PFOA/APFO with support from two non-guidleine studies on the tumorigenesis of PFDA.
RAC's response
Noted.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2015	France		MemberState	5
Comment received				
Additional human data on PFDA have not been included in the report: The association between PFDA and endometriosis was examined, but no difference in mean serum levels was found between US women with the disease (n = 190) (GM = 0.20 ng/mL) and controls (n = 283) (GM = 0.18 ng/mL). The AOR of an endometriosis diagnosis were increased per logarithm unit change for PFDA (AOR = 2.6, 95 % CI = 0.62-10.9) in women undergoing surgery, although this was not statistically significant (Louis et al., 2012). Louis GMB, Peterson CM, Chen Z, Hediger ML, Croughan MS, Sundaram R, Stanford JB, Fujimoto VY, Varner MW, Giudice LC, Kennedy A, Sun L, Wu Q and Kannan K, 2012. Perfluorochemicals and Endometriosis The ENDO Study. Epidemiology, 23, 799-805. Joensen et al. (2009) observed no difference in mean serum levels in 105 men with high testosterone (0.9 ng/mL) and those with low (0.8 ng/mL). Joensen UN, Bossi R, Leffers H, Jensen AA, Skakkeb aek NE and Jorgensen N, 2009. Do perfluoroalkyl compounds impair human semen quality? Environ Health Perspect, 117, 923-927. Vestergaard et al. (2012) reported that among 430 couples with no children, serum concentrations did not differ among those women who became pregnant (0.11 ng/mL) and those that did not (0.10 ng/mL). Vestergaard S, Nielsen F, Andersson AM, Hjollund NH, Grandjean P, Andersen HR and Jensen TK, 2012. Association between perfluorinated compounds and time to pregnancy in a prospective cohort of Danish couples attempting to conceive. Hum Reprod, 27, 873-880. Similarly, Louis et al. (2013) reported that serum levels had no effect on couple fecundity (n = 501). Louis GM, Sundaram R, Schisterman EF, Sweeney AM, Lynch CD, Gore-Langton RE, Maisog J, Kim S, Chen Z and Barr DB, 2013. Persistent Environmental Pollutants and Couple Fecundity: The LIFE Study. Environmental health perspectives, 121, 231-236. Christensen et al. (2011), who examined the effect of maternal levels on the age of the offspring girl‛s menarche in the ALSPAC study, reported that all measurements were below the level of detection (LOD; 0.2 ng/mL). Christensen KY, Maisonet M, Rubin C, Holmes A, Calafat AM, Kato K, Flanders WD, Heron J, McGeehin MA and Marcus M, 2011. Exposure to polyfluoroalkyl chemicals during pregnancy is not associated with offspring age at menarche in a contemporary British cohort. Environment international, 37, 129-135. It might be useful to include these date and to discuss how they may influence the classification proposal for reprotoxicity.				

A study on mice (Johansson et al., 2008), not included in the CLH report, also compared PFDA and PFOA. As PFOA is used in a read across approach as the source chemical, it could be useful to mention this study. In this study, the authors reported that, in contrast to effects observed with PFOA and PFOS, oral gavage treatment of 10-day-old NMRI mouse pups with a single dose of 1.4 or 21 µmol/kg b.w. (0.75 or 11.3 mg/kg b.w.) PFDA did not affect body weight, clinical signs or behavioural parameters at age 2 and 4 months.
Johansson N, Fredriksson A and Eriksson P, 2008. Neonatal exposure to perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) causes neurobehavioural defects in adult mice. NeuroToxicology, 29, 160-169.

Dossier Submitter's Response

Thank you for highlighting additional human studies on PFCAs including PFDA on reproductive toxicity. They could complement the list of references in the background document where relevant.

The classification proposal of Repr 1B (dev tox) and Repr 2 (fertility) is based on evidence from animal studies and relies on read-across from APFO/PFOA with support from PFNA. The database for classification is considered reliable since it has already been evaluated by RAC (APFO/PFOA have harmonised classification; RAC opinion for PFNA was adopted). Read-across from PFOA to PFDA is considered approporiate based on structural similarities, a common functional group and in that they are relatively strong acids that are expected to dissociate to their respective anionic forms at physiological pH and are thus expected to be available to cells in the form of their corresponding carboxylate anion (PFD and PFO, respectively).

<u>Fertility</u>
Effects of APFO/PFOA, PFNA and PFDA found in animal studies on fertility relates to sperm morphology and testosterone levels. Below are the basis for the classification in Repr. 2 for fertility extracted from the RAC opinion for PFNA (ECHA 2014):
- minor effects (small reductions in sperm motility and sperm count in epididymis of F0 males, but not in F1 males) without reductions in mating or fertility indexes with the mixture S-111-S-WB which has PFNA as major constituent, in a 2-generation study (Stump et al., 2008);
- increase in serum testosterone levels, decrease in serum estradiol levels and increased frequency of spermatogenic cells with apoptotic features in rats exposed by gavage to 5 mg PFNA/kg/d (Feng et al., 2009);
- reduced plasma testosterone concentrations, increased frequency of abnormalities in sperm morphology and vacuolated cells in the seminiferous tubules of 129/sv wild-type (mPPARα) and hPPARα mice exposed orally to APFO for 6 weeks, although these effects could be mediated in part by liver peroxisome proliferation, since they were not observed in similarly exposed Pparα-null mice (Li et al., 2011), and
- the supporting preliminary human data [note by DS: Joensen et al., 2009]

Joensen et al., 2009 investigated the association between PFAAs, including PFDA, and testosterone levels and found no significant difference in serum concentrations of PFDA; PFNA, or PFOA in groups of men with high or low testosterone levels, respectively.
This study has been assessed in the RAC opinion for PFNA and included as supportive data for effects on fertility and is therefore also included in the current dossier:
'Out of all examined PFAAs, the highest concentrations were found for perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS), PFOA and PFNA (medians of 24.5, 6.6, 4.9, and 0.8 ng/mL, respectively). The high serum concentrations of PFAAs were significantly associated with reduced numbers of normal spermatozoa. In addition, sperm

concentration, total sperm count, and sperm motility showed some tendency toward lower levels in men with high PFAA levels, although not at statistically significant levels. The authors noted that the results from this preliminary study should be corroborated in larger studies." (RAC opinion CLH PFNA, ECHA 2014).

In a very recent publication that came out in the beginning of 2015 (after the data collection for producing the current dossier; study not indiated by the French CA), Louis et al (Louis GM, Chen Z, Schisterman EF, Kim S, Sweeney AM, Sundaram R, Lynch CD, Gore-Langton RE, Barr DB. Perfluorochemicals and human semen quality: the LIFE study. Environ Health Perspect. 2015 Jan;123(1):57-63) reported that PFDA, PFNA, PFOA, and PFOS were associated with a lower percentage of sperm with coiled tails. These findings are in line with animal studies pointing to effects on certain semen endpoints.

We note the additional human studies mentioned in this comment by the French CA: Louis et al., 2012; Joensen et al., Vestergaard et al., 2012. The samples in the studies are quite small and we consider that the findings should be interpreted with caution. The data may give som indications on the association between serum levels and effects, however, they do not give any information on the causal relationship. Further, the findings are not considered to compromise appropriatness of the read-across from APFO/PFOA and PFNA to PFDA for fertility.

<u>Development</u>
Christensen et al 2011 investigated the association between maternal serum concentrations of PFCs, including PFDA, and the age of the offspring girl's menarche. Since all levels of PFDA were below the level of detection (LOD; 0.2 ng/mL) no conclusion can be made for PFDA in this study. Moreover, none of the PFCs measured in the serum from the girls' mothers during pregnancy appeared to be associated with age at menarche in this cohort. Thererfore, we consider this study as not useful to include as supportive data for the reproductive toxicicty of PDFA.

Johansson et al., 2008 investigated the neurobehaviuoral effects after administration of a single dose of PFOS, PFOA or PFDA in male mice pups at PND 10. No neurobehavioural defects of PFDA was detected at the age 2 or 4 months in contrast to PFOA or PFOS. This data indicates that read-across from PFOA to PFDA for developmental neurotoxicity could be questioned. However, the implications of this data for the appropriatness of read-across from PFOA to PFDA for developmental toxicity is unclear. The classification of PFOA in Repr 1B for development is not based on findings on adverse effects on developmental neurotoxicity. The available information on APFO/PFOA and PFNA indicates that exposure during gestation reduces pup viability, pup body weight gain, delays puberty as well as the onset of eye opening, increases both dam and pup liver weight (absolute and relative liver weight) and causes full litter resorptions at higher doses (RAC opinion CLH PFNA, ECHA 2014).

RAC's response

The RAC, after reviewing these additional studies, acknowledged that, from the extensive literature of perfluorinated compounds, some studies can provide further support while others could not reach sufficient sample size to conclude (or provided negative associations), but also considered that the DS's analysis is thorough and carefully developed, paying attention to providing a global clear picture of the data (including both studies that provided evidence that PFDA was found in breast milk and studies where it was not found) and therefore that the CLH report contained an appropriate dataset.

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2015	Germany		MemberState	6
Comment received				
PFDA was investigated in a non-guideline study in mice. The treatment yielded in a dose-dependent decrease in fetal body weight per litter from 1.12 mg/kg/day. Additionally, a read across was performed to PFOA.				
Dossier Submitter's Response				
Thank you for your comment. We note the German CA support earlier in comment number 3 and agrees to their observation that the classification of PFDA as developmental toxicant relies on read-across to PFOA/APFO with support from one non-guideline pre-natal developmental toxicity study of PFDA in mice.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2015	Germany		MemberState	7
Comment received				
It is recommended that the read across considerations should also include STOT RE 1 as this endpoint was not addressed by the self classification.				
Dossier Submitter's Response				
Thank you for your comment. Please see our response in comment number 2.				
RAC's response				
The RAC has assessed the hazard classes for which data were provided in the CLH report and which were open for comments during the public consultation.				