



**Committee for Risk Assessment  
RAC**

Annex 2  
**Response to comments document (RCOM)**  
to the Opinion proposing harmonised classification and  
labelling at Community level of  
**Perfluorooctanoic acid (PFOA)**

**ECHA/RAC/DOC No CLH-O-0000002227-78-01/A2**

**Adopted**  
**2 December 2011**

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON  
PERFLUOROOCTANOIC ACID (PFOA)**

---

**COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION**

*[ECHA has compiled the comments received via internet that refer to several hazard classes and entered them under each of the relevant categories/headings as comprehensive as possible. Please note that some of the comments might occur under several headings when splitting the given information is not reasonable.]*

**Substance Name:** Perfluorooctanoic acid (PFOA)  
**EC Number:** 206-397-9  
**CAS Number:** 335-67-1

**Note:**

There is no comment in the public consultation that addressed or questioned the validity of directly using the toxicological data from APFO for the assessment of PFOA.

Some of the comments referred to endpoint-specific classification proposals. However, these comments are not specific for PFOA; they relate to the toxicological APFO data and were submitted identically in the context of the APFO public consultation.

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON  
PERFLUOROOCTANOIC ACID (PFOA)**

---

**General comments**

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comments
17/01/2011	UK / Kevin Thurlow / LGC / Company-Manufacturer	The name should be ammonium pentadecafluorooctanoate, or ammonium perfluorooctanoate according to IUPAC rules.	Corrected	
09/02/2011	France / Member State	<p>The recommendations agreed at the TC C&amp;L regarding the classification of APFO (ammonium pentadecafluorooctanoate) for human health are supported in agreement with the classification proposed in the CLH report, taking into account the new studies performed and published after the final discussion of the classification proposal at the TC C&amp;L in October 2006.</p> <p>These new studies consolidate the rationale for classification as Repr 1B – H360D. More particularly the similarity between human and mice data, which both shows the placental barrier crossing, the accumulation of APFO or PFOA in the embryo, and the lack of sex-difference in APFO or PFOA elimination. Thereby, the outcomes from mice recent studies have more weight in the decision on classification and support classification as Repr 1B – H360D.</p>	<p>Thank you for the support</p> <p>Noted.</p>	
18/02/2011	Sweden / Ing-Marie Olsson / MemberState	Sweden supports the proposed classification of Ammonium pentadecafluorooctanoate (APFO) (CAS Number 3825-26-1) as the proposal was previously agreed on by the Technical Committee on Classification and Labelling (Directive 67/548/EEC) ('TC C&L') and the new data give added support for the proposed classification.	Thank you for the support.	Noted.
21/02/2011	UK MemberState /	<p>We understand that this is a 'transition substance' for which the C&amp;L was previously agreed by the TC C&amp;L. Consequently, the comments submitted below are observations intended to ease the progress of APFO through the new CLP harmonised classification and labelling system.</p> <p>We support the proposed classification according to DSD as previously agreed at the TC C&amp;L.</p> <p>We support the proposed classification according to CLP but we believe Acute Tox 4 (H332) should be applied instead of Acute Tox 3 (H331). Please refer to our comments in the section for other hazard classes.</p>	<p>Thank you for the support.</p> <p>Is changed to acute tox 4 H332, see comment in section for other hazard classes.</p>	Points were considered.
21/02/2011	Germany / Bernd Niedersträßer / MemberState /	<p>Comment for the German CA:</p> <p>We agree to the proposed classification. From previous cases not finalised in the TC C&amp;L it appears that referring to the previous discussions was not sufficient for the justification of community wide action regarding endpoints other than CMR and resp. sensitisation. Therefore, substantiating the justification should be considered.</p>	Thank you for the support.	Extended justification is now included.

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON  
PERFLUOROOCTANOIC ACID (PFOA)**

---

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comments
		In addition, the data of the standard information in the CLH-dossier pursuant to Annex VII are incomplete. Although the physico-chemical properties are not relevant for the classification and labelling we recommend the use of the "data waiver" because of the plausibility in the CLH dossier.	Thank you for the information. Relevant data are included in the dossier.	
		In section '1.2 Composition' the molecular formula is incorrect and should be revised to C8-H4-N-F15-O2	Corrected	
21/02/2011	Denmark / Peter Hammer Sørensen / MemberState	As the classification of ammonium pentadecaflurooctanoate (APFO) was agreed in the former TC C&L group, Denmark supports the proposed classification	Thank you for the support.	Noted.

**Carcinogenicity**

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment
18/02/2011	Ireland / Health & Safety Authority	The Irish CA is in agreement with the proposed classification Carc. Cat. 3 R40 (Carc. 2 H351), as previously agreed by TC C&L in 2006.	Thank you for the support	Noted.
21/02/2011	UK/ MemberState	We support the proposal to classify APFO as Carc Cat 3; R40, as previously agreed at TC C&L, and Carc. 2 (H351) in accordance with CLP.	Thank you for the support	Noted.

**Mutagenicity**

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comment
21/02/2011	UK / MemberState	We agree that the data on mutagenicity do not support classification for this endpoint.	Thank you for the support	Noted.

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON  
PERFLUOROOCTANOIC ACID (PFOA)**

---

**Toxicity to reproduction**

/Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment
18/02/2011	Netherlands / RIVM Bureau REACH / National Authority	<p>Fertility</p> <p>In a 2 generation study in rats, no effects were found on fertility parameters. Although some effects were found on epididymis and seminal vesicles, they were probably the result of substance-induced weight loss (organ to body weight ratios were normal or increased) and therefore not relevant. In repeated dose studies in several species, no relevant effects on reproductive organs were reported. We therefore agree with no classification for fertility.</p> <p>Development</p> <p>According to the TC C&amp;L (October 2006), mouse studies are more relevant than rat studies, since the renal clearance is lower in mice than in rats and is even lower in humans. Several studies in mice are reported that address developmental toxicity.</p> <p>In the developmental study by Lau et al, (2006) (doses of 0, 1, 3, 5, 10, 20 and 40 mg/kg bw on GD 1-17), dams showed increased body weight at doses <math>\geq</math> 20 mg/kg bw. In addition, all treated groups showed increased liver weight (further liver parameters were not analysed). No further maternal toxicity was observed. The following effects were observed in pups: advanced puberty onset males (<math>\geq</math> 1 mg/kg bw), growth retardation (<math>\geq</math> 3 mg/kg bw), increased full litter resorption (<math>\geq</math> 5 mg/kg bw), delayed eye opening (<math>\geq</math> 5 mg/kg bw), reduced ossification (<math>\geq</math> 1 mg/kg bw (not as reported in the annex VI dossier only in the 10 and 20 mg/kg bw groups)), decreased number of live fetuses (<math>\geq</math> 20 mg/kg bw), decreased fetal body weight (<math>\geq</math> 20 mg/kg bw).</p> <p>In the study by Wolf et al. (2007) (cross-fosterpart: doses of 0, 3 and 5 mg/kg bw on GD 1-17; restricted exposure part: 5 or 20 mg). Dam bodyweight was not adversely affected. Liver weight was increased in both treated groups (further liver parameters were not analysed). In utero exposure in the absence of lactational exposure was sufficient to produce postnatal body weight deficits and developmental delay in the pups. Effects on pup survival from birth to weaning were only affected in litters exposed to 5 mg/kg bw in utero and during lactation. Pups exposed on GD7-17 and 10-17 also showed developmental delay in eye opening and hair growth.</p> <p>In 2 studies by White et al. (2007 and 2009) (doses of 0 and 5 mg/kg bw/day), all exposed female pups displayed stunted mammary epithelial branching and growth at between PND 1 and 63, both after lactation- or intra uterine-only exposure. No effects on maternal body weights were observed. Liver effects were not analysed.</p> <p>Maternal toxicity in these developmental studies was limited to reduced body weight (gain) and increased liver weight. Also in repeated dose toxicity studies liver toxicity was observed. Hepatocellular hypertrophy, degeneration and/or focal to multifocal necrosis were reported with increases in severity between doses of 1.5 to 15 mg/kg bw/day in rats and mice. Classification as Xn; R 48/22 was based on liver toxicity in both mice and rats as demonstrated in several studies. Thus, the results on liver toxicity are considered substance related toxicity (and not only an adaptive response).</p>	<p>The text concerning ossification has been modified in the CLH report</p> <p>New information has been included</p>	Studies have been addressed accordingly.

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON  
PERFLUOROOCTANOIC ACID (PFOA)**

---

/Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment
		<p>Increased liver weight was observed in dams at all exposure concentrations (i.e. also at the lower doses). Unfortunately, further liver parameters were not analysed in the developmental studies in mice. Since similar doses are used in the developmental studies as in the repeated dose studies, similar effects cannot be excluded. Since the proposed classification for developmental toxicity is based on the studies in mice, we think it is necessary to discuss in the CLH report the likelihood that the observed developmental effects in the developmental studies in mice are secondary to liver toxicity.</p> <p>Abbott et al. (2007) studied the influence of PPAR<math>\alpha</math> on PFOA-induced developmental toxicity (WT and PPAR<math>\alpha</math>-ko mice, doses up to 20 mg APFO/kg bw/day on GD1-17). In this study, full litter resorptions increased at the 5 mg/kg bw/day dose in both WT and KO mice (note that liver weight was increased at doses <math>\geq</math> 1 (WT) and 3 (KO) mg/kg bw). In contrast, the study indicated that several of the other developmental effects in mice are influenced by PPAR<math>\alpha</math> (post-natal lethality, delayed eye opening and deficits in postnatal weight gain). These effects occur only in WT and also at doses where no increased liver weight is observed. They may therefore be not secondary to liver toxicity. The effects may therefore be caused via PPAR<math>\alpha</math>. However, since humans do not respond to PPAR<math>\alpha</math> stimulation in the same way as rodents, these effects (that may not be secondary to liver toxicity) may not be relevant for humans. The relevance of PPAR<math>\alpha</math> related effects for humans should be discussed in the CLH report.</p>	<p>in the CLH report. Please see response to comments from Industry</p> <p>The discussion of PPAR<math>\alpha</math> and human relevance has been extended in the CLH report. Please see response to comments from Industry</p>	
21/02/2011	UK MemberState /	We support the proposal to classify APFO as Repr Cat 2; R61, as previously agreed at TC C&L, and Repr. 1B (H360) in accordance with CLP.	Thank you for the support	Noted.

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON  
PERFLUOROOCTANOIC ACID (PFOA)**

---

/Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment
21/02/2011	Germany / Bernd Niederstädter / MemberState	<p>Comment for the German CA:</p> <p>p.37 study by Abbott 2007: please clarify whether full litter resorptions occurred only at or also above the doses (at 5 mg/kg)</p> <p>p. 39 conclusion on Developmental toxicity: It is stated that different findings in rats and mice are likely to be due to different kinetics. Since this does not follow necessarily from the study descriptions or the toxicokinetics section, substantiation would be appreciated.</p> <p>Classification of PFOA and its salts was discussed in the TC C&amp;L. The data available since were added to the current proposal and support the classification proposed. Nevertheless it should be contemplated whether the conclusion should be extended by some considerations on the mode/mechanism of action of reprotoxic effects and its relevance for humans. It appears that some effects are PPAR<math>\alpha</math> mediated (e.g. post-natal lethality), which might not be considered of relevance for the human situation, whereas other effects (e.g. early embryonic loss) can be mediated by other receptors and human relevance cannot be ruled out. This might be helpful for the discussion.</p> <p>You might want to consider the addition of the following studies:</p> <p>Fei C et al. (2007): Perfluorinated chemicals and fetal growth: A study within the Danish National Birth Cohort. Environ. Health Perspectives;</p> <p>Apelberg et al.: Determinants of fetal exposure to polyfluoroalkyl compounds in Baltimore, Maryland. Environ Sci Technol 2007, 41, 3891-3897;</p> <p>Apelberg et al.: Cord serum concentrations of perfluorooctanoate sulfonate (PFOS) and perfluorooctanoate (PFOA) in relation to weight and size at birth. Environ Health Perspect, 2007b, 115, 670-1676.</p> <p>Grice et al.: Self-reported medical conditions in perfluorooctanesulfonyl fluoride manufacturing workers. J Occup Environ Med 2007, 49, 722-729.</p>	<p>Text has been modified in the CLH report. Full litter resorptions occurred at doses <math>\geq</math>5 mg/kg</p> <p>The discussion of PPAR<math>\alpha</math> and human relevance has been extended in the CLH report. Please see response to Industry</p>	Noted.
21/02/2011	Denmark / Peter Hammer Sørensen / MemberState	<p>The new available data on developmental toxicity (Wolf et al., 2007), (White et al., 2007,2009), (Yang et al., 2009), (Fenton et al., 2009) and (Abbot et al., 2007) together with the human study (Midasch 2007) had become available after the decision from the TC C&amp;L group. The studies mostly confirm the effects of APFO exposure on mammary gland development in mice.</p> <p>Epidemiological studies are considered inconclusive and thus not relevant for classification purpose.</p> <p>Based on the data available at the time being, the classification for developmental reprotoxicity in cat. 2 (Repr.1B) seems to be most appropriate.</p>	Thank you for the support	Agreed.
17/02/2011	Belgium Mike Neal / Plastics Europe / Industry or trade association	<p><i>ECHA's comment: The text below is copied from the attachment 110216PlasticsEurope Submission Norway CLP.pdf</i></p> <p>Norwegian Proposed Classification of Ammonium Pentadecafluorooctanoic Acid (APFO), Norwegian Proposed Classification - PFOA and its salts other than APFO.</p>	Industry has raised some important questions related to the classification of APFO/PFOA for	Noted.

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON  
PERFLUOROOCTANOIC ACID (PFOA)**

/Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment
		<p>The PlasticsEurope Fluoropolymers Committee wishes to make comments on the Norwegian proposals for the classification and labelling of ammonium pentadecafluorooctanoic acid (APFO).</p> <p>A key element of the Norwegian proposal is to classify APFO for developmental effects into Category 1b based on the GHS criteria (Repr. 1B, H360D - Repr. Cat. 2; R61 using the criteria of the Directive 67/548/EEC). These comments address developmental toxicity (Section 5.9.2) only. Specific comments on other portions of the Norwegian proposal are not addressed in these comments. The full proposal was commented on previously 8th September 2006 (see File No. ECB-I-18-06 16-02-11). It should be noted that an equivalent proposal has been prepared for perfluorooctanoic acid (PFOA) and its salts, and PlasticsEurope would like to stress that the comments made on APFO developmental toxicity apply equally to the proposal for PFOA and its salts other than APFO.</p> <p>It is the position of PlasticsEurope that there is insufficient evidence to warrant classification of APFO or of PFOA and its other salts into GHS Category 1b for developmental effects (Directive 67/548/EEC Category 2). The scientific points presented in the attached comments relate to the influence of maternal effects on developmental outcomes in the studies used to support the Norwegian proposal, the appropriateness of rodent species for the developmental hazard assessment of APFO for humans based on recent mode of action data, and the lack of consistent associations of PFOA with developmental effects in 21 published human epidemiological studies. PlasticsEurope's comments conclude that the weight of evidence suggests that classification into GHS Category 2 (Directive 67/548/EEC Category 3) for this endpoint is the most appropriate classification.</p> <p>Yours faithfully, M A Neal Secretary to PlasticsEurope Fluoropolymer Committee</p> <hr/> <p>Comments on the Norwegian Proposed Classification of Ammonium Pentadecafluorooctanoic Acid (APFO) for Developmental Toxicity Submitted by PlasticsEurope</p> <p>The Norwegian proposal</p> <p>The Norwegian proposal is to classify ammonium pentadecafluorooctanoic acid (APFO, CASRN 3825-26-1, EC 223-320-4) for developmental effects with Repr. Cat. 2; R61. According to CLP Regulation, it is proposed APFO is Repr. 1B, H360D. This proposed classification is based on the increased postnatal pup mortality, decreased pup body weight, and delayed sexual maturation observed in the mouse2, as well as in the rat 2-generation study, in the absence of marked maternal toxicity.</p>	developmental toxicity, some of which have also been touched upon by the Netherlands and by Germany. Based on the increase in liver weight in dams observed also at lower exposure doses and the apparent role of PPAR $\alpha$ for developmental toxicity, Industry has proposed the classification of APFO/PFOA in Repr Cat 2 instead of Repr Cat 1B. Data has been lacking to properly address the possible influence on developmental toxicity of increased maternal liver weight and the relevance of PPAR $\alpha$ -mediated developmental effects for humans. However, since the former version of the CLH report,	

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON  
PERFLUOROOCTANOIC ACID (PFOA)**

/Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment
		<p>It should be noted that an equivalent proposal has been prepared for perfluorooctanoic acid (PFOA) and its salts3. At the beginning of section 1 of the proposal for PFOA it is stated that:</p> <p><i>"PFOA is used as a group name for PFOA and its salts , and PFOA is mainly produced and used as its ammonium salt, [ammonium pentadecafluorooctanoate] (APFO, CAS Number: 3825-26-1). However, the perfluorooctanoate anion is the molecule of primary interest. APFO and PFOA are sometimes used interchangeably as both PFO-anion and PFOA (neutral species) exist in solution. For systemic effects it might be assumed that both substances (APFO and PFOA) are mainly available to cells with its physiological pH in form of the corresponding anion (PFO). That might be the central justification for read across for systemic effects."</i></p> <p>Therefore, the comments made here apply equally to the proposal for PFOA and its salts other than APFO.</p> <p>A number of additional studies on the developmental effects of APFO have become available since the classification was originally proposed and discussed in the ECB meeting (2007). These studies provide further information on the role of maternal effects, mode of action, and human relevance of the developmental effects of APFO seen in laboratory studies. The significance of these newer findings to the proposed classification warrants a re-evaluation of the classification.</p> <p><b>Position of PlasticsEurope</b></p> <p>It is the position of PlasticsEurope that there is insufficient evidence to warrant classification of APFO (and PFOA and its other salts) in Category 2 (Category 1B for GHS) for developmental effects and that the weight of evidence suggests that classification Category 3 (Category 2 for GHS) for this endpoint is the most appropriate. The effects cited in support of the proposal by Norway (increased pup mortality, decreased pup body weight, and delayed sexual maturation) occurred at dose levels that either produced effects in the maternal animal that produced an influence on developmental endpoints or that produced non-developmentally-specific direct toxicity to offspring. Furthermore, evaluation of the mode of action of effects observed in the offspring of mice has identified a significant role for activation of the xenosensor nuclear receptor, peroxisome proliferator activated receptor <math>\alpha</math> (PPAR<math>\alpha</math> - also known as NR1C1), bringing into question the human relevance of effects mediated by this receptor in mice and rats. As a result, the mouse and rat may not be the most appropriate species for the hazard assessment of the impact of APFO on developmental toxicity in humans. In addition, there are a number of studies in humans addressing various aspects of developmental toxicity which show no association between adverse effects and exposure, albeit at low levels, to the chemical. PlasticsEurope, therefore, encourages that the classification for developmental hazards take into consideration the full weight of the evidence for potential developmental effects, specifically to include the human relevance of mode of action data as well as evidence from human epidemiological studies.</p> <p><b>Maternal toxicity</b></p> <p>In the Norwegian Proposal, it is concluded that developmental effects associated with APFO occurred in the</p>	<p>several new studies have been published and some of these shed light on the causes of developmental toxicity. New data have now been included in the CLH report to discuss these recent insights. Below the most relevant results from the new studies are shortly presented. The Norwegian MS has performed a careful evaluation of the new data and in our opinion the originally proposed classification of APFO (and PFOA) for developmental toxicity (Repr 1B, H360D) is strengthened by the newly published studies. Furthermore, the very long half-life of PFOA in humans compared to rodents and the efficient placental</p>	

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON  
PERFLUOROOCTANOIC ACID (PFOA)**

---

/Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment
		<p>absence of marked maternal toxicity. However, the experimental evidence suggests that this statement is incorrect and that the effects cited are observed only at doses higher than those producing significant effects in the maternal animal. Guidance from the European Union, Section 3.7.2.4.1. states:</p> <p>“Development of the offspring throughout gestation and during the early postnatal stages can be influenced by toxic effects in the mother either through non-specific mechanisms related to stress and the disruption of maternal homeostasis, or by specific maternally-mediated mechanisms.”</p> <p>In fact, several lines of evidence suggest the involvement of maternal toxicity, as seen in the disruption of maternal homeostasis, in the outcome of the developmental toxicity studies in the mouse. These include the following:</p> <ol style="list-style-type: none"> <li>1) Statistically significant (<math>p &lt; 0.05</math>), dose-related increases in maternal liver weight were observed at a dose as low as 1 mg/kg in the mouse study by Lau et al. (2006) (see Table A). Similarly, a more recent mouse study by Yahia et al. (2010) demonstrated statistically significantly (<math>p &lt; 0.05</math>) increased maternal liver weight relative to body weight at a dose of 1 mg/kg, and increased absolute and relative liver weights at the two higher doses administered, 5 and 10 mg/kg. In both the Lau et al. (2006) and Yahia et al. (2010) studies, maternal liver weight responses were present at doses lower than those affecting the fetus/neonate.</li> <li>2) When the influence of liver enlargement is accounted for by subtracting liver weight from whole-body weight, dose-related decreases in mean maternal body weight compared to controls were apparent at all PFOA doses based on data obtained from the mouse study by Lau et al. (2006), with statistical significance at doses of 3 mg/kg and higher (Table A) 4. In the mouse study by Yahia et al. (2010), statistically significant maternal body weight deficits were observed at both doses (5 and 10 mg/kg) at which fetal/neonatal effects were observed.</li> <li>3) Maternal effects on the maintenance of pregnancy: The resorption of entire litters observed by Lau et al. (2006) and Wolf et al. (2007) appears to be maternally-mediated rather than a direct fetotoxic response. Wolf et al. (2007) reported litter losses when APFO was given from GD 1 – 17 but none when the same dose was given from GD 7 – 17, suggesting that the effect was related to altered maternal implantation. In a study investigating the mechanism of full litter loss, Lau et al. (2005) reported that total implantations were not affected in CD mice given 20 mg/kg from GD 1 – 8; although, the percent viable implants was reduced on GD 7 and 8. Using embryo culture with PFOA concentrations in media ranging from 100 – 1250 µg/mL, Lau et al. (2005) demonstrated that PFOA was capable of disrupting embryonic development at concentrations of 400 µg/mL and above, with 100% lethality occurring at the highest concentration tested. Lau et al. state that the mouse embryonic effects in culture occur at PFOA concentrations much higher than those in mouse maternal serum which were associated with early full-litter loss. Based on serum PFOA concentration data provided to PlasticsEurope by Dr. Christopher Lau, the mean <math>\pm</math> SD mouse maternal serum PFOA concentration at the lowest dose at which early full litter resorption occurred (5 mg/kg) was <math>71.91 \pm 8.33</math> µg/mL. Based on a study of placental transfer pharmacokinetics of PFOA in rats by Hinderliter et al. (2005), it is reasonable to infer that PFOA concentrations achieved in mouse embryos during gestational exposure of mouse dams are considerably less than those achieved in maternal serum. Because effects on embryos in culture occurred at concentrations of 400 µg/mL and higher, these observations lend</li> </ol>	<p>transfer of PFOA gives a high concern for human exposure. Although role of the human PPAR<math>\alpha</math> in developmental toxicity of AFPO/PFOA is still not clear, we believe that there is sufficient data to maintain the Repr Cat 1B classification.</p>	<p>Maternal body weights in the Yahia study were only affected at 10 mg/kg.</p>

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON  
PERFLUOROOCTANOIC ACID (PFOA)**

---

/Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment
		<p>support to the notion that PFOA-induced pregnancy loss in the mouse most likely is associated with maternal factors. Lau et al. concluded that “these studies suggest that the PFOA-induced pregnancy loss in the mouse is likely associated with maternal factors and/or a critical stage of the embryonic development during the periimplantation period, and may explain the relatively low teratogenic potential of PFOA in the in vivo study.”</p> <p>In the Yahia et al. (2010) mouse study, early full-litter resorptions were not observed at doses up to 10 mg/kg, in contrast to the study by Lau et al. (2006) where full litter resorptions were observed at doses of 5 mg/kg and above. It is apparent that significant maternal toxicity was encountered in all test groups studied in mice, and that the fetal effects observed are a reflection of these maternal responses.</p> <p>The developmental toxicity of APFO has also been studied in the rat (Butenhoff et al., 2004; Gortner, 1981; Staples et al., 1984) and rabbit (Gortner, 1982). In these studies, no increase in malformations relative to controls was observed at oral doses up 150 mg/kg/day in rats and 50 mg/kg/day in rabbits, as well as inhalation concentrations up to 25 mg/m<sup>3</sup> (6 h/d). In the studies by Gortner and by Staples et al., any effects on fetal or pup weight were present at dose levels equivalent to or higher than those causing weight effects or other toxicities in the maternal animals. In a two-generation reproduction/developmental study in rats (Butenhoff et al., 2004), the highest dose group (30 mg/kg) F1-generation pups had decreased birth weight and reduced viability that were in apparent relationship to reduced body weight at birth and weaning. These latter effects are similar to those observed in mice by Lau et al. (2006) and Abbott et al. (2007), and it is reasonable to infer that this may also be due to the influence of PPAR<math>\alpha</math> activation.</p> <p><b>Postnatal Pup Mortality and Body Weight</b> In the Norwegian Proposal, the classification is, in part, based on the observation of decreased postnatal pup body weight and survival, effects which were seen in the mouse studies by Lau et al. (2006) and Wolf et al. (2007). It is stated also that these effects were seen in the absence of marked maternal toxicity. Again, this latter statement is incorrect, as the evidence suggests that the effects are only seen in the presence of significant maternal toxicity (<i>vide supra</i>). The recent mouse study by Yahia et al. (2010) lends additional support to the premise that the observed effects are secondary to effects on the maternal mouse.</p> <p><b>Sexual Maturation</b> In the Norwegian Proposal, the classification is, in part, based on the observation of delayed sexual maturation in rodents (Butenhoff et al., 2004; Lau et al., 2006). It is also stated that these effects were seen in the absence of marked maternal toxicity. Again, this latter statement is incorrect, as the evidence suggests that the effects are generally only seen in the presence of significant maternal toxicity (<i>vide supra</i>). In the mouse (Lau et al., 2006), pubertal development for the female mouse was not appreciably affected by prenatal PFOA treatment. Only a slight delay was noted in the highest dose group (20 mg/kg) with either age at vaginal opening or time to first estrus. In contrast, the onset of puberty for the male mice was markedly advanced</p>		

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON  
PERFLUOROOCTANOIC ACID (PFOA)**

---

/Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment
		<p>(not delayed, as stated in the proposal) by PFOA in groups receiving from 1 to 10 mg/kg. It is noteworthy that this accelerated pubertal maturation took place despite a body weight deficit of 25 – 30%. It should be noted that at the highest dose tested (20 mg/kg), male maturation showed a slight delay. It is also noted in the Norwegian Proposal, that the effects on male sexual maturation are described as “accelerated pubertal malformation”. There is no evidence that any malformation in the development of male sexual organs has ever been reported.</p> <p>In the rat (Butenhoff <i>et al.</i>, 2004), preputial separation and vaginal opening were somewhat delayed at 30 mg/kg (no effect seen in 10 mg/kg or lower). The influence of body weight deficits on sexual maturation is well-described in the literature. Butenhoff <i>et al.</i> examined the possible 110216 Submission Norway CLP Page 6 of 14 role of reduced body weight by covarying body weight at weaning with days to sexual maturation in F1 pups and found no significant differences in days to sexual maturation between controls and treated rats.</p> <p><b>Mode of Action and Relevance for Humans</b></p> <p>Recent studies provide evidence that many of the observed effects of PFOA exposure, including those observed in developing mice, are mediated by the xenosensor nuclear receptor PPAR<math>\alpha</math>. Because PPAR<math>\alpha</math> may not play a critical role in normal development (Braissant <i>et al.</i>, 1996; Lee <i>et al.</i>, 1995), and in that it is generally recognized that humans are considerably less sensitive to the effects of PPAR<math>\alpha</math> activation (Klaunig <i>et al.</i>, 2003; Lake, 2009), the recent observations bring into question the relevance of mouse (and rat) effects known to be mediated by PPAR<math>\alpha</math>. Abbott <i>et al.</i> (2007) studied the influence of nuclear receptor peroxisome proliferator activated receptor <math>\alpha</math> (PPAR<math>\alpha</math> also known as NR1C1) on the developmental effects of APFO in the Sv/129 mouse strain. They studied the effect of APFO dosing during pregnancy on developmental endpoints using 129S1/SvlmJ wild-type (WT) mice and Ppara-tm1Gonz/J PPAR<math>\alpha</math> knock-out mice (KO) based on the closely matched 129S4/SvJae strain. Both pup mortality and pup weight, endpoints critical to the proposed classification, were unaffected in the KO model, while these endpoints were affected in the WT. These data suggest that PPAR<math>\alpha</math> is involved in mediating these particular effects of APFO on pup development. In addition, the data suggest a potential role of PPAR<math>\alpha</math> in mediating early full-litter resorption, as the NOELs for full-litter resorption in WT and KO mice were 0.3 and 3 mg/kg, respectively. While these data suggest a major role for PPAR<math>\alpha</math> in mediating reduced body weight, survival, and early full-litter loss, it is not possible to rule out completely the contribution of other modes of action to these findings. For example, the liver hypertrophic response to PPAR<math>\alpha</math> activation would be expected to be absent in the KO mice and their pups if PPAR<math>\alpha</math> were the sole mediator of effects. However, increased relative liver weight was observed in both WT and KO maternal mice and their pups at approximately the same doses in the Abbott <i>et al.</i> study. This hypertrophic effect likely is mediated by the constitutive androstane receptor (CAR (also known as NR1I3)) and the pregnane X receptor (PXR (also known as NR1I2)) (Elcombe <i>et al.</i>, 2010; Rosen <i>et al.</i>, 2009).</p> <p>It is well-documented that APFO-induced effects in rodent liver are largely the result of PPAR<math>\alpha</math> activation with some contribution from activation of the constitutive androstane receptor (CAR (also known as NR1I3)) and the pregnane X receptor (PXR (also known as NR1I2)) (Elcombe <i>et al.</i>, 2010; Rosen <i>et al.</i>, 2009). It has also been</p>		

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON  
PERFLUOROOCTANOIC ACID (PFOA)**

---

/Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment
		<p>established that human liver is less responsive to the pleiotrophic effects of activation of PPAR_ (Klaunig <i>et al.</i>, 2003; Lake, 2009). In transgenic mice in which the endogenous mouse forms of PPAR_ and CAR have been replaced by the human forms, it has been demonstrated further that activation of the human forms of the PPAR_and CAR receptor do not produce the proliferative response in the liver that is observed with the endogenous mouse forms of the same receptors (Gonzalez and Shah, 2008; Ross <i>et al.</i>, 2010). Thus, with respect to PPAR_-mediated and CAR-mediated effects in both the liver and intermediary metabolism, the human response is either attenuated or absent as compared to that of the rodent.</p> <p>Although PPAR_ is expressed in fetal rodent and human tissues (Abbott, 2009), studies with PPAR_ KO mice suggest that PPAR_ is not required for embryonic survival and development (Lee <i>et al.</i>, 1995). This would suggest that activation of PPAR_-mediated effects in mouse fetuses or neonates most likely would result in inducing peroxisome proliferation, hepatomegaly, and up-regulation of lipid metabolism, all known effects of PPAR_ in adults. Although, specific comparative information on gestational expression of PPAR_ in human fetal tissues is limited primarily to gastrointestinal tissues (Abbott, 2009), the general attenuation of the response to activation of PPAR_ in humans as contrasted to rodents would suggest that PPAR_-mediated developmental effects are of less relevance to humans.</p> <p>In a rat 2-generation reproductive study (Butenhoff <i>et al.</i>, 2004), marginal effects on pup mortality and pup weight were observed. A non-statistically significant increase in F1-generation pup mortality, but not in the F2-generation, was observed at the highest dose used in that experiment (30 mg/kg). At the same dose, reduced body weight was observed in the F1 pups and F2 pups at birth and throughout lactation; although, the effect was only statistically significant in the F1-generation at birth and prior to weaning. These effects were not seen at doses of 10 mg/kg or lower. The role of PPAR<math>\alpha</math> in these effects in the rat is not known.</p> <p><b>Human Studies</b></p> <p>The classification proposal makes reference to several human epidemiological studies analyzing possible association between concentrations of PFOA in maternal or fetal blood and birth outcomes. The consideration of human data is consistent with European Union guidance (see Section 3.7.2.3.1.) which states:</p> <p><i>“Classification as a reproductive toxicant is made on the basis of an assessment of the total weight of evidence, see section 1.1.1. This means that all available information that bears on the determination of reproductive toxicity is considered together, such as epidemiological studies and case reports in humans and specific reproduction studies along with sub-chronic, chronic and special study results in animals that provide relevant information regarding toxicity to reproductive and related endocrine organs.”</i></p> <p>The classification document considered the human epidemiological studies to be inconclusive.</p> <p>On the contrary, these studies bring useful insights into potential developmental hazard to humans, albeit when exposed to low concentrations of APFO. Included among these studies are well-conducted studies involving a population having significantly higher serum PFOA levels than the general human population.</p>		

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON  
PERFLUOROOCTANOIC ACID (PFOA)**

---

/Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment
		<p>Studies by Apelberg <i>et al.</i> (2006; 2007) on birth weight and the levels of two perfluoroalkyls (PFOA and PFOS) in umbilical cord blood initiated a series of research papers regarding human developmental outcomes and, subsequently, reproductive parameters. As is often a trend in the epidemiological literature, the initial published papers on a topic are suggestive of associations. However, it is only through a series of research studies that an understanding of the weight of the evidence emerges. In this regard, 21 papers have been published pertaining to human reproductive and developmental outcomes in populations exposed to perfluoroalkyl acids, including two literature reviews (Olsen <i>et al.</i>, 2009; Steenland <i>et al.</i>, 2010).</p> <p>Besides gestational age and birth weight, there have been other developmental outcomes that have been examined across these studies. Table B presents a summary of the epidemiological studies, the endpoints studied, and their statistical significance. As can be seen, no developmental outcome is consistently reported as being statistically significantly associated with exposure to PFOA.</p> <p><b>Conclusion</b></p> <p>In conclusion, there is insufficient evidence to warrant classification of APFO or of PFOA and its other salts in Category 2 (Category 1B for GHS) for developmental effects. The effects cited in support of the proposal by Norway (increased pup mortality, decreased pup body weight, and delayed sexual maturation) occurred at maternally toxic dose levels. Furthermore, the mouse may not be the most appropriate species for the hazard assessment of the impact of APFO on developmental toxicity in humans based on recent mode of action data. Developmental studies in rats and rabbits have not shown effects (Lau <i>et al.</i>, 2004). In addition, there are a number of studies in humans (Table B) addressing various aspects of developmental toxicity which show no association between adverse effects and exposure, albeit at low levels, to the chemical. Thus, the weight of evidence suggests that classification Category 3 (Category 2 for GHS) for this endpoint is the most appropriate.</p>		

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON  
PERFLUOROOCTANOIC ACID (PFOA)**

/Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment																																																																						
		<p><b>Table A:</b>          Maternal body weight, liver weight, liver weight as a percent of body weight, body weight minus liver weight, gravid uterine weight, body weight minus gravid uterine weight, and body weight minus gravid uterine weight and liver weight in female CD1 mice dosed during gestation in study reported by Lau <i>et al.</i> (2006)<sup>a</sup>.</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th></th><th colspan="6" style="text-align: center;">Dose Group (mg/kg)</th></tr> <tr> <th></th><th style="text-align: center;">0</th><th style="text-align: center;">1</th><th style="text-align: center;">3</th><th style="text-align: center;">5</th><th style="text-align: center;">10</th><th style="text-align: center;">20</th></tr> </thead> <tbody> <tr> <td>Group Size (N)</td><td style="text-align: center;">40</td><td style="text-align: center;">14</td><td style="text-align: center;">16</td><td style="text-align: center;">20</td><td style="text-align: center;">14</td><td style="text-align: center;">5</td></tr> <tr> <td>Body Weight<sup>b</sup> (BW), g</td><td style="text-align: center;"><math>54.36 \pm 6.50</math></td><td style="text-align: center;"><math>52.62 \pm 3.06</math></td><td style="text-align: center;"><math>52.01 \pm 6.81</math></td><td style="text-align: center;"><math>50.51 \pm 4.49^*</math></td><td style="text-align: center;"><math>51.68 \pm 7.31</math></td><td style="text-align: center;"><math>38.24 \pm 7.73^{**}</math></td></tr> <tr> <td>Liver Weight<sup>c</sup> (LW), g</td><td style="text-align: center;"><math>2.45 \pm 0.28</math></td><td style="text-align: center;"><math>3.18 \pm 0.28^{***}</math></td><td style="text-align: center;"><math>4.30 \pm 0.51^{***}</math></td><td style="text-align: center;"><math>4.66 \pm 0.56^{***}</math></td><td style="text-align: center;"><math>5.44 \pm 0.77^{***}</math></td><td style="text-align: center;"><math>5.36 \pm 0.77^{***}</math></td></tr> <tr> <td>LW:BW ratio<sup>d</sup>, %</td><td style="text-align: center;"><math>4.53 \pm 0.47</math></td><td style="text-align: center;"><math>6.07 \pm 0.80^{***}</math></td><td style="text-align: center;"><math>8.39 \pm 1.40^{***}</math></td><td style="text-align: center;"><math>9.27 \pm 1.28^{***}</math></td><td style="text-align: center;"><math>10.65 \pm 1.66^{***}</math></td><td style="text-align: center;"><math>14.18 \pm 1.65^{***}</math></td></tr> <tr> <td>BW – LW<sup>e</sup>, g</td><td style="text-align: center;"><math>51.91 \pm 6.33</math></td><td style="text-align: center;"><math>49.45 \pm 3.22</math></td><td style="text-align: center;"><math>47.70 \pm 6.74^*</math></td><td style="text-align: center;"><math>45.85 \pm 4.44^{**}</math></td><td style="text-align: center;"><math>46.24 \pm 7.01^{**}</math></td><td style="text-align: center;"><math>32.88 \pm 7.15^{***}</math></td></tr> <tr> <td>Uterine Weight<sup>f</sup> (UW), g</td><td style="text-align: center;"><math>21.38 \pm 4.01</math></td><td style="text-align: center;"><math>20.95 \pm 2.62</math></td><td style="text-align: center;"><math>17.71 \pm 5.45^{**}</math></td><td style="text-align: center;"><math>17.24 \pm 3.09^{**}</math></td><td style="text-align: center;"><math>17.56 \pm 3.83^{**}</math></td><td style="text-align: center;"><math>10.56 \pm 5.00^{**}</math></td></tr> <tr> <td>BW – UW<sup>g</sup>, g</td><td style="text-align: center;"><math>32.99 \pm 3.04</math></td><td style="text-align: center;"><math>31.67 \pm 1.71</math></td><td style="text-align: center;"><math>34.29 \pm 2.67</math></td><td style="text-align: center;"><math>33.27 \pm 3.04</math></td><td style="text-align: center;"><math>34.11 \pm 4.33</math></td><td style="text-align: center;"><math>27.68 \pm 3.88^{**}</math></td></tr> <tr> <td>BW – LW – UW<sup>h</sup>, g</td><td style="text-align: center;"><math>30.54 \pm 2.85</math></td><td style="text-align: center;"><math>28.50 \pm 1.71</math></td><td style="text-align: center;"><math>29.99 \pm 2.40</math></td><td style="text-align: center;"><math>28.61 \pm 2.96</math></td><td style="text-align: center;"><math>28.68 \pm 3.98</math></td><td style="text-align: center;"><math>22.32 \pm 3.34^{**}</math></td></tr> </tbody> </table> <p>* Statistically significant (<math>p \leq 0.05</math>) ** Statistically significant (<math>p \leq 0.01</math>) *** Statistically significant (<math>p \leq 0.001</math>)</p> <p><sup>a</sup> Lau <i>et al.</i> (2006) Effects of perfluorooctanoic acid exposure during pregnancy in the mouse. Toxicol Sci 90, 510-518. Raw data from this study were kindly provided by Dr. Christopher Lau, United States Environmental Protection Agency. The results of analyses presented in Table A were prepared by PlasticsEurope. PlasticsEurope acknowledges the assistance of Dr. David Gaylor in conducting statistical analyses of the data.</p> <p><sup>b</sup> Pooled standard deviation for maternal body weight was 6.06 g.</p> <p><sup>c</sup> Coefficient of variation for liver weight was 0.118.</p> <p><sup>d</sup> Coefficient of variation for liver weight as a percent of body weight was 0.129.</p> <p><sup>e</sup> Pooled standard deviation for body weight minus liver weight was 5.95 g.</p> <p><sup>f</sup> Gravid uterine weight. Pooled standard deviation for gravid uterine weight was 3.98 g.</p> <p><sup>g</sup> Pooled standard deviation for maternal body weight minus gravid uterine weight was 3.09 g.</p> <p><sup>h</sup> Pooled standard deviation for maternal body weight minus liver weight and minus gravid uterine weight was 2.89 g.</p> <p>Note: In preparing Table A, dose-response data for maternal body weight, gravid uterine weight, and liver weight were subjected to statistical tests in order to determine which doses produced significant differences from the control group. For those effects where standard deviations were relatively constant across dose groups, an improved estimate of the standard deviation was obtained based on the pooled variance across dose groups. For maternal liver weight and liver weight relative to the body weight, the standard deviation increased as liver weight increased. However, the coefficient of variation (standard deviation / mean) was relatively constant across dose groups. Hence, a pooled estimate of the coefficient of variation across dose groups was used to obtain improved estimates of the standard deviations for liver weight and liver weight expressed as a percent of body weight. Since body and organ weights are approximately normally distributed, two-sided t-tests were employed to compare dose group means with the control mean. Since five dose groups were compared with controls, a modified Bonferroni multiple comparisons procedure was employed which accommodates unequal sample sizes (Hochberg and Lachenbruch, 1976). Maternal body weight including an adjustment for gravid uterine weight produced statistically significant differences from controls only at the highest dose (20 mg/kg).</p> <p>Maternal liver weight, absolute and relative to body weight, showed dose-response trends with the lowest dose (1 mg/kg) statistically significantly different from controls.</p>		Dose Group (mg/kg)							0	1	3	5	10	20	Group Size (N)	40	14	16	20	14	5	Body Weight <sup>b</sup> (BW), g	$54.36 \pm 6.50$	$52.62 \pm 3.06$	$52.01 \pm 6.81$	$50.51 \pm 4.49^*$	$51.68 \pm 7.31$	$38.24 \pm 7.73^{**}$	Liver Weight <sup>c</sup> (LW), g	$2.45 \pm 0.28$	$3.18 \pm 0.28^{***}$	$4.30 \pm 0.51^{***}$	$4.66 \pm 0.56^{***}$	$5.44 \pm 0.77^{***}$	$5.36 \pm 0.77^{***}$	LW:BW ratio <sup>d</sup> , %	$4.53 \pm 0.47$	$6.07 \pm 0.80^{***}$	$8.39 \pm 1.40^{***}$	$9.27 \pm 1.28^{***}$	$10.65 \pm 1.66^{***}$	$14.18 \pm 1.65^{***}$	BW – LW <sup>e</sup> , g	$51.91 \pm 6.33$	$49.45 \pm 3.22$	$47.70 \pm 6.74^*$	$45.85 \pm 4.44^{**}$	$46.24 \pm 7.01^{**}$	$32.88 \pm 7.15^{***}$	Uterine Weight <sup>f</sup> (UW), g	$21.38 \pm 4.01$	$20.95 \pm 2.62$	$17.71 \pm 5.45^{**}$	$17.24 \pm 3.09^{**}$	$17.56 \pm 3.83^{**}$	$10.56 \pm 5.00^{**}$	BW – UW <sup>g</sup> , g	$32.99 \pm 3.04$	$31.67 \pm 1.71$	$34.29 \pm 2.67$	$33.27 \pm 3.04$	$34.11 \pm 4.33$	$27.68 \pm 3.88^{**}$	BW – LW – UW <sup>h</sup> , g	$30.54 \pm 2.85$	$28.50 \pm 1.71$	$29.99 \pm 2.40$	$28.61 \pm 2.96$	$28.68 \pm 3.98$	$22.32 \pm 3.34^{**}$		
	Dose Group (mg/kg)																																																																									
	0	1	3	5	10	20																																																																				
Group Size (N)	40	14	16	20	14	5																																																																				
Body Weight <sup>b</sup> (BW), g	$54.36 \pm 6.50$	$52.62 \pm 3.06$	$52.01 \pm 6.81$	$50.51 \pm 4.49^*$	$51.68 \pm 7.31$	$38.24 \pm 7.73^{**}$																																																																				
Liver Weight <sup>c</sup> (LW), g	$2.45 \pm 0.28$	$3.18 \pm 0.28^{***}$	$4.30 \pm 0.51^{***}$	$4.66 \pm 0.56^{***}$	$5.44 \pm 0.77^{***}$	$5.36 \pm 0.77^{***}$																																																																				
LW:BW ratio <sup>d</sup> , %	$4.53 \pm 0.47$	$6.07 \pm 0.80^{***}$	$8.39 \pm 1.40^{***}$	$9.27 \pm 1.28^{***}$	$10.65 \pm 1.66^{***}$	$14.18 \pm 1.65^{***}$																																																																				
BW – LW <sup>e</sup> , g	$51.91 \pm 6.33$	$49.45 \pm 3.22$	$47.70 \pm 6.74^*$	$45.85 \pm 4.44^{**}$	$46.24 \pm 7.01^{**}$	$32.88 \pm 7.15^{***}$																																																																				
Uterine Weight <sup>f</sup> (UW), g	$21.38 \pm 4.01$	$20.95 \pm 2.62$	$17.71 \pm 5.45^{**}$	$17.24 \pm 3.09^{**}$	$17.56 \pm 3.83^{**}$	$10.56 \pm 5.00^{**}$																																																																				
BW – UW <sup>g</sup> , g	$32.99 \pm 3.04$	$31.67 \pm 1.71$	$34.29 \pm 2.67$	$33.27 \pm 3.04$	$34.11 \pm 4.33$	$27.68 \pm 3.88^{**}$																																																																				
BW – LW – UW <sup>h</sup> , g	$30.54 \pm 2.85$	$28.50 \pm 1.71$	$29.99 \pm 2.40$	$28.61 \pm 2.96$	$28.68 \pm 3.98$	$22.32 \pm 3.34^{**}$																																																																				

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON  
PERFLUOROOCTANOIC ACID (PFOA)**

/Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment																																																																																																																																																																																																																																														
		<p><b>Table B: Summary of associations from studies of human reproductive and developmental outcomes related to PFOA exposure.</b></p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th>Endpoint</th><th>Olsen <i>et al.</i> (2004)</th><th>Grice <i>et al.</i> (2007)</th><th>Inoue <i>et al.</i> (2004)</th><th>Apelberg <i>et al.</i> (2006; 2007)</th><th>Fei <i>et al.</i> (2009; 2008a; 2010; 2008b; 2007)</th><th>Monroy <i>et al.</i> (2008)</th><th>Washino <i>et al.</i> (2009)</th><th>Hamm <i>et al.</i> (2010)</th><th>Nolan <i>et al.</i> (2010; 2009)</th><th>Stein <i>et al.</i> (2009)</th><th>Christiansen <i>et al.</i> (2011)</th><th>Fletcher (2010)</th><th>Ander- sen <i>et al.</i> (2010)</th></tr> </thead> <tbody> <tr> <td>Gestational Age</td><td></td><td>N.S.</td><td></td><td>N.S.</td><td>N.S.</td><td>N.S.</td><td></td><td>N.S.</td><td>N.S.</td><td>N.S.</td><td></td><td></td><td></td></tr> <tr> <td>Birth Weight</td><td></td><td>N.S.</td><td>N.S.</td><td>N.S.</td><td>S.S.</td><td>N.S.</td><td>N.S.</td><td>N.S.</td><td>N.S.</td><td>N.S.</td><td></td><td></td><td></td></tr> <tr> <td>Birth Length</td><td></td><td></td><td></td><td>N.S.</td><td>S.S.</td><td></td><td>N.S.</td><td></td><td></td><td></td><td></td><td></td><td></td></tr> <tr> <td>Head Circumference</td><td></td><td></td><td></td><td></td><td>S.S.</td><td>N.S.</td><td></td><td>N.S.</td><td></td><td></td><td></td><td></td><td></td></tr> <tr> <td>Abdominal/chest Circumference</td><td></td><td></td><td></td><td></td><td>S.S.</td><td></td><td>N.S.</td><td></td><td></td><td></td><td></td><td></td><td></td></tr> <tr> <td>Apgar Score</td><td></td><td></td><td></td><td></td><td></td><td>N.S.</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr> <tr> <td>Ponderal Index</td><td></td><td></td><td></td><td></td><td>S.S.</td><td>N.S.</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr> <tr> <td>Placental Weight</td><td></td><td></td><td></td><td></td><td></td><td>N.S.</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr> <tr> <td>Miscarriage</td><td>N.S.</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>N.S.</td><td></td><td></td><td></td><td></td></tr> <tr> <td>Birth Defects (nonspecific)</td><td>N.S.</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>N.S.</td><td>N.S.</td><td></td><td></td><td></td></tr> <tr> <td>Preeclampsia</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>N.S.</td><td></td><td></td><td></td></tr> <tr> <td>Body Weight &amp; BMI through 12 mos.</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>S.S.</td><td></td></tr> <tr> <td>Developmental Milestones</td><td></td><td></td><td></td><td></td><td>N.S.</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr> <tr> <td>Sexual Maturation</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>N.S.</td><td>S.S.</td><td></td><td></td></tr> <tr> <td>Infectious Disease in Early Childhood</td><td></td><td></td><td></td><td></td><td>N.S.</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr> <tr> <td>Subfecundity</td><td></td><td></td><td></td><td></td><td>S.S.</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr> </tbody> </table> <p>Key: N.S. = not a statistically significant result (<math>p \geq 0.05</math>); S.S. = statistically significant result (<math>p &lt; 0.05</math>)</p> <p><b>Citations</b></p> <p>Abbott, B. D., et al. (2007). Perfluorooctanoic acid (PFOA)-induced developmental toxicity in the mouse is dependent on expression of peroxisome proliferator activated receptor-alpha (PPAR<math>\alpha</math>). <i>Toxicol Sci</i> <b>98</b>, 571-81.</p> <p>Abbott, B. D. (2009). Review of the expression of peroxisome proliferator activated receptors alpha (PPAR<math>\alpha</math>), beta (PPAR<math>\beta</math>), and gamma (PPAR<math>\gamma</math>) in rodent and human development. <i>Reproductive Toxicology</i> <b>27</b>.</p> <p>Andersen, C. S., et al. (2010). Prenatal exposures to perfluorinated chemicals and anthropometric measures in infancy. <i>Am J Epidemiol</i> <b>172</b>, 1230-1237.</p> <p>Apelberg, B. J. (2006). Fetal Exposure to Perfluorinated Compounds: Distribution and determinants of exposure and relationships with weight and size at birth, Ed.^ Eds.), pp. 1-222. Johns Hopkins, Baltimore.</p> <p>Apelberg, B. J., et al. (2007). Cord serum concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) in relation to weight and size at birth. <i>Environ Health Perspect</i> <b>115</b>, 1670-1676.</p> <p>Braissant, O., et al. (1996). Differential expression of peroxisome proliferator-activated receptors (PPARs): tissue</p>	Endpoint	Olsen <i>et al.</i> (2004)	Grice <i>et al.</i> (2007)	Inoue <i>et al.</i> (2004)	Apelberg <i>et al.</i> (2006; 2007)	Fei <i>et al.</i> (2009; 2008a; 2010; 2008b; 2007)	Monroy <i>et al.</i> (2008)	Washino <i>et al.</i> (2009)	Hamm <i>et al.</i> (2010)	Nolan <i>et al.</i> (2010; 2009)	Stein <i>et al.</i> (2009)	Christiansen <i>et al.</i> (2011)	Fletcher (2010)	Ander- sen <i>et al.</i> (2010)	Gestational Age		N.S.		N.S.	N.S.	N.S.		N.S.	N.S.	N.S.				Birth Weight		N.S.	N.S.	N.S.	S.S.	N.S.	N.S.	N.S.	N.S.	N.S.				Birth Length				N.S.	S.S.		N.S.							Head Circumference					S.S.	N.S.		N.S.						Abdominal/chest Circumference					S.S.		N.S.							Apgar Score						N.S.								Ponderal Index					S.S.	N.S.								Placental Weight						N.S.								Miscarriage	N.S.								N.S.					Birth Defects (nonspecific)	N.S.								N.S.	N.S.				Preeclampsia										N.S.				Body Weight & BMI through 12 mos.												S.S.		Developmental Milestones					N.S.									Sexual Maturation										N.S.	S.S.			Infectious Disease in Early Childhood					N.S.									Subfecundity					S.S.										All references were checked, relevant references were considered by Dossier submitter (see appendix to BD)
Endpoint	Olsen <i>et al.</i> (2004)	Grice <i>et al.</i> (2007)	Inoue <i>et al.</i> (2004)	Apelberg <i>et al.</i> (2006; 2007)	Fei <i>et al.</i> (2009; 2008a; 2010; 2008b; 2007)	Monroy <i>et al.</i> (2008)	Washino <i>et al.</i> (2009)	Hamm <i>et al.</i> (2010)	Nolan <i>et al.</i> (2010; 2009)	Stein <i>et al.</i> (2009)	Christiansen <i>et al.</i> (2011)	Fletcher (2010)	Ander- sen <i>et al.</i> (2010)																																																																																																																																																																																																																																					
Gestational Age		N.S.		N.S.	N.S.	N.S.		N.S.	N.S.	N.S.																																																																																																																																																																																																																																								
Birth Weight		N.S.	N.S.	N.S.	S.S.	N.S.	N.S.	N.S.	N.S.	N.S.																																																																																																																																																																																																																																								
Birth Length				N.S.	S.S.		N.S.																																																																																																																																																																																																																																											
Head Circumference					S.S.	N.S.		N.S.																																																																																																																																																																																																																																										
Abdominal/chest Circumference					S.S.		N.S.																																																																																																																																																																																																																																											
Apgar Score						N.S.																																																																																																																																																																																																																																												
Ponderal Index					S.S.	N.S.																																																																																																																																																																																																																																												
Placental Weight						N.S.																																																																																																																																																																																																																																												
Miscarriage	N.S.								N.S.																																																																																																																																																																																																																																									
Birth Defects (nonspecific)	N.S.								N.S.	N.S.																																																																																																																																																																																																																																								
Preeclampsia										N.S.																																																																																																																																																																																																																																								
Body Weight & BMI through 12 mos.												S.S.																																																																																																																																																																																																																																						
Developmental Milestones					N.S.																																																																																																																																																																																																																																													
Sexual Maturation										N.S.	S.S.																																																																																																																																																																																																																																							
Infectious Disease in Early Childhood					N.S.																																																																																																																																																																																																																																													
Subfecundity					S.S.																																																																																																																																																																																																																																													

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON  
PERFLUOROOCTANOIC ACID (PFOA)**

---

/Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment
		<p>distribution of PPAR-alpha, -beta, and -gamma in the adult rat. <i>Endocrinology</i> <b>137</b>, 354-66.</p> <p>Butenhoff, J. L., et al. (2004). The reproductive toxicology of ammonium perfluorooctanoate (APFO) in the rat. <i>Toxicology</i> <b>196</b>, 95-116.</p> <p>Christensen, K. Y., et al. (2011). Exposure to polyfluoroalkyl chemicals during pregnancy is not associated with offspring age at menarche in a contemporary British cohort. <i>Environ Int</i> <b>37</b>, 129-135.</p> <p>Elcombe, C. R., et al. (2010). Hepatocellular hypertrophy and cell proliferation in Sprague-Dawley rats following dietary exposure to ammonium perfluorooctanoate occurs through increased activation of the xenosensor nuclear receptors PPAR<math>\alpha</math> and CAR/PXR. <i>Arch Toxicol</i> <b>84</b>, 787-798.</p> <p>Fei, C., et al. (2007). Perfluorinated chemicals and fetal growth: a study within the Danish National Birth Cohort. <i>Environ Health Perspect</i> <b>115</b>, 1677-1682.</p> <p>Fei, C., et al. (2008a). Prenatal exposure to PFOA and PFOS and maternally reported developmental milestones in infancy. <i>Environ Health Perspect</i> <b>116</b>, 1391-1395.</p> <p>Fei, C., et al. (2008b). Fetal growth indicators and perfluorinated chemicals: A study in the Danish National Birth Cohort. <i>Am J Epidemiol</i> <b>168</b>, 66-72.</p> <p>Fei, C., et al. (2009). Maternal levels of perfluorinated chemicals and subfecundity. <i>Human Reproduction</i> <b>24</b>, 1200-1205.</p> <p>Fei, C., et al. (2010). Prenatal exposure to PFOA and PFOS and risk of hospitalization for infectious diseases in early childhood. <i>Environmental Research</i> <b>110</b>, 773-777.</p> <p>Fletcher (2010). Patterns of age of puberty among children in the Mid-Ohio Valley in relation to perfluorooctanoic acid (PFOA) and perfluorooctanesulfonate (PFOS). Briefing notes. <a href="http://www.C8sciencepanel.org">www.C8sciencepanel.org</a>.</p> <p>Gonzalez, F. J. and Shah, Y. M. (2008). PPAR<math>\alpha</math>: mechanism of species differences and hepatocarcinogenesis of peroxisome proliferators. <i>Toxicology</i> <b>246</b>, 2-8.</p> <p>Gortner, E. G. (1981). Oral teratology study of T-2998CoC in rats. Experiment Number 0681TR0110. Safety Evaluation Laboratory and Riker Laboratories, Inc., St. Paul, MN. USEPA Public Docket, AR-226-0463. 110216 Submission Norway CLP Page 13 of 14</p> <p>Gortner, E. G. (1982). Oral teratology study of T-3141CoC in rabbits. Experiment Number 0681TB0398. Safety Evaluation Laboratory and Riker Laboratories, Inc., St. Paul, MN. USEPA Public Docket AR-226-0465.</p> <p>Grice, M. M., et al. (2007). Self-reported medical conditions in perfluorooctanesulfonyl fluoride manufacturing workers. <i>J Occup Environ Med</i> <b>49</b>, 722-9.</p> <p>Hamm, M. P., et al. (2010). Maternal exposure to perfluorinated acids and fetal growth. <i>Journal of Exposure Science and Environmental Epidemiology</i> <b>20</b> 589-597.</p> <p>Hinderliter, P. M., et al. (2005). Perfluorooctanoate: Placental and lactational transport pharmacokinetics in rats. <i>Toxicology</i> <b>211</b>, 139-48.</p> <p>Hochberg, Y. and Lachenbruch, P. A. (1976). Two stage multiple comparison procedures based on the studentized range. <i>Commun Stat A</i> <b>5</b>, 1447-1453.</p> <p>Inoue, K., et al. (2004). Perfluorooctane sulfonate (PFOS) and related perfluorinated compounds in human</p>		

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON  
PERFLUOROOCTANOIC ACID (PFOA)**

---

/Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment
		<p>maternal and cord blood samples: assessment of PFOS exposure in a susceptible population during pregnancy. <i>Environ Health Perspect</i> <b>112</b>, 1204-7.</p> <p>Klaunig, J. E., et al. (2003). PPARalpha agonist-induced rodent tumors: modes of action and human relevance. <i>Crit Rev Toxicol</i> <b>33</b>, 655-780.</p> <p>Lake, B. G. (2009). Species differences in the hepatic effects of inducers of CYP2B and CYP4A subfamily forms: relationship to rodent liver tumour formation. <i>Xenobiotica</i> <b>39</b>, 582-96.</p> <p>Lau, C., et al. (2004). The developmental toxicity of perfluoroalkyl acids and their derivatives. <i>Toxicol Appl Pharmacol</i> <b>198</b>, 231-41.</p> <p>Lau, C., et al. (2005). Pregnancy loss associated with exposure to perfluorooctanoic acid in the mouse. <i>Birth Defects Research (Part A)</i> <b>73</b>, 358.</p> <p>Lau, C., et al. (2006). Effects of perfluorooctanoic acid exposure during pregnancy in the mouse. <i>Toxicol Sci</i> <b>90</b>, 510-518.</p> <p>Lee, S. S., et al. (1995). Targeted disruption of the alpha isoform of the peroxisome proliferatoractivated receptor gene in mice results in abolishment of the pleiotropic effects of peroxisome proliferators. <i>Mol Cell Biol</i> <b>15</b>, 3012-22.</p> <p>Monroy, R., et al. (2008). Serum levels of perfluoroalkyl compounds in human maternal and umbilical cord blood samples. <i>Environ Res</i> <b>108</b>, 56-62.</p> <p>Nolan, L. A., et al. (2009). The relationship between birth weight, gestational age and perfluorooctanoic acid (PFOA)-contaminated public drinking water. <i>Reprod Toxicol</i> <b>27</b>, 231-238.</p> <p>Nolan, L. A., et al. (2010). Congenital anomalies, labor/delivery complications, maternal risk factors and their relationship with perfluorooctanoic acid (PFOA)-contaminated public drinking water. <i>Reprod Toxicol</i> <b>29</b>, 147-155.</p> <p>Olsen, G. W., et al. (2004). Serum concentrations of perfluorooctanesulfonate and other fluorochemicals in an elderly population from Seattle, Washington. <i>Chemosphere</i> <b>54</b>, 1599-611.</p> <p>Olsen, G. W., et al. (2009). Perfluoroalkyl chemicals and human fetal development: an epidemiologic review with clinical and toxicological perspectives. <i>Reprod Toxicol</i> <b>27</b>, 212-30.</p> <p>Rosen, M. B., et al. (2009). Does exposure to perfluoroalkyl acids present a risk to human health? <i>Toxicol Sci</i> <b>111</b>, 1-3.</p> <p>Ross, J., et al. (2010). Human constitutive androstane receptor (CAR) and pregnane X receptor (PXR) support the hypertrophic but not the hyperplastic response to the murine nongentoxic hepatocarcinogens phenobarbital and chlordane <i>in vivo</i>. <i>Toxicol Sci</i> <b>116</b>, 452-466. 110216 Submission Norway CLP Page 14 of 14</p> <p>Staples, R. E., et al. (1984). The embryo-fetal toxicity and teratogenic potential of ammoniumperfluorooctanoate (APFO) in the rat. <i>Fundam Appl Toxicol</i> <b>4</b>, 429-40.</p> <p>Steenland, K., et al. (2010). Epidemiologic Evidence on the Health Effects of Perfluorooctanoic Acid (PFOA). <i>Environ Health Perspect</i> <b>118</b>, 1100-1108.</p> <p>Stein, C. R., et al. (2009). Serum levels of perfluorooctanoic acid and perfluorooctane sulfonate and pregnancy outcome. <i>Am J Epidemiol</i> <b>170</b>, 837-846.</p>		

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON  
PERFLUOROOCTANOIC ACID (PFOA)**

---

/Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment
		<p>Washino, N., et al. (2009). Correlations between prenatal exposure to perfluorinated chemicals and reduced fetal growth. <i>Environ Health Perspect</i> <b>117</b>, 660-667.</p> <p>Wolf, C. J., et al. (2007). Developmental toxicity of perfluorooctanoic acid in the CD-1 mouse after cross-foster and restricted gestational exposures. <i>Toxicol Sci</i> <b>95</b>, 462-73.</p> <p>Yahia, D., et al. (2010). Effects of perfluorooctanoic acid (PFOA) exposure to pregnant mice on reproduction. <i>The Journal of Toxicological Sciences</i> <b>35</b>, 527-533.</p>		

**Respiratory sensitisation**

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment

**Other hazards and endpoints**

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment
18/02/2011	Ireland / Health & Safety Authority	<p>Acute Toxicity:</p> <p>The Irish CA agrees with the acute toxicity classification of Xn; R20/22 for PFOA, as previously agreed by TC C&amp;L in 2006.</p> <p>However, from the information presented in the dossier, we are of the opinion that the translation of R22 to CLP Acute Toxicity 3 H301 is not justified. The proposed CLP classification is based upon a range test which determined the LD50 to lie between 250 and 500mg/kg bw in female SD rats; the weight of evidence from the other studies reported is that the LD50 exceeds 400mg/kg bw in female rats which would result in a CLP classification of Acute Tox 4 H302.</p> <p>The Irish CA is in agreement with the CLP classification for Acute toxicity (inhalation), Acute tox 3 H331.</p>	<p>This classification is borderline between Acute Toxicity 3 H301 and Acute toxicity 4 H302. However, we consider Acute Toxicity 3 H301 to be appropriate, since the lowest LD 50 values cited are around 250 mg/kg. Further several of the tests indicating a higher LD 50 value did not perform tests at</p>	Comments considered.

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON  
PERFLUOROOCTANOIC ACID (PFOA)**

---

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment
		<p>Irritation: The Irish CA is in agreement with the proposed classification Xi R36 (Eye Irrit. 2 H319), as previously agreed by TC C&amp;L in 2006.</p> <p>Repeat dose toxicity: The Irish CA is in agreement with the proposed classification T; R48/23, Xn R48/22, as previously agreed by TC C&amp;L in 2006. For CLP classification of the repeat dose toxicity (STOT) hazard class, we suggest it is sufficient to classify the substance as STOT RE1, H372 only, with the accompanying hazard statement: "STOT RE 1 H372: Causes damage to organs (liver) through prolonged or repeated exposure." The route of exposure only needs to be specified if it is conclusively proven that no other routes of exposure cause the hazard: in this case both oral and inhalation exposure lead to hepatotoxicity- with strong indications that dermal exposure also leads to hepatotoxicity. Consequently the STOT-RE 2 classification for oral exposure is redundant.</p>	<p>multiple dose levels.</p> <p>We agree that STOT RE 2 is redundant. STOT RE 2 is deleted since this already is covered by STOT RE 1.</p>	
21/02/2011	UK MemberState /	<p>Page 15- Acute toxicity- Inhalation- we understand that the classification of APFO as Xn; R20 (<math>1 &lt; LC50 \leq 5</math> mg/l/4 hr), was agreed at the TC C&amp;L, based on discrepancies in the results (<math>&gt;4.5</math> and <math>0.98</math> mg/l/4 hr) and the borderline value (<math>0.98</math> mg/l/4 hr) of the second study between toxic and harmful. Therefore, we believe that, following the same logic, the corresponding classification according to the CLP criteria, should be Acute Tox Category 4 (H332) (<math>1.0 &lt; ATE \leq 5.0</math>), instead of the proposed Acute Tox Category 3 (H331) (<math>0.5 &lt; ATE \leq 1</math>).</p> <p>Page 15 – Acute Toxicity – For completeness, a section addressing the new endpoint, STOT-SE, should be included in this Annex VI proposal.</p>	<p>We agree. To be in line with the interpretation of the data made in the TC C&amp;L group the classification is changed to category 4.</p> <p>Since only lethality was reported, a classification with STOT SE is not proposed.</p>	Has been considered.
21/02/2011	Germany / Bernd Niederst&ber / MemberState	<p>Comment for the German CA:</p> <p>The summary and discussion on skin irritation should contain a clear statement whether classification is proposed or not (watch out for copy&amp;paste mistakes – APFO/PFOA).</p>	Corrected in the CLH dossier, no classification is	

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON  
PERFLUOROOCTANOIC ACID (PFOA)**

---

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment
		<p>1.3 Physico-chemical properties, Table 1: Summary of physico-chemical properties</p> <p>VII, 7.2, Melting/freezing point: The information regarding decomposition is unclear since two different decomposition temperatures are mentioned and the melting point is above the decomposition point.</p> <p>VII, 7.9, Flash point: The flash point does not need to be tested because the substance is a solid.</p> <p>VII, 7.10, Flammability: Flammability upon ignition (solids): no data available Flammability on contact with water: The classification procedure needs not to be applied because the organic substance does not contain metals or metalloids. Pyrophoric properties: The classification procedure needs not to be applied because the organic substance is known to be stable into contact with air at room temperature for prolonged periods of time (days).</p> <p>VII, 7.11, Explosive properties: The classification procedure needs not to be applied because there are no chemical groups present in the molecule which are associated with explosive properties.</p> <p>VII, 7.12, Self-ignition temperature for solids: The study does not need to be conducted for solids, because the substance has a melting point &lt; 160°C.</p> <p>VII, 7.13; Oxidising properties of solids: The classification procedure needs not to be applied because the organic substance contains oxygen and fluorine, which are chemically bonded only to carbon.</p> <p>6. Human health hazard assessment of physico-chemical properties</p> <p>6.1 Explosivity No classification for explosivity is proposed.</p>	<p>proposed.</p> <p>Thank you for the information. Relevant parts are included in the dossier.</p>	

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON  
PERFLUOROOCTANOIC ACID (PFOA)**

---

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comment
		6.2 Flammability No classification for flammability is proposed.  6.3 Oxidising potential No classification for oxidising properties is proposed.		

*Attachments:*

Plastics Europe / Mike Neal: *110216PlasticsEurope Submission Norway CLP.pdf* (included in the table above)

Plastics Europe / Mike Neal: *Document in ECB-I-18-06 16-02-11 - FC-143a.pdf*

Plastics Europe / Mike Neal: *Document in ECB-I-18-06 16-02-11 - FC-143b Frame FLUOROS.pdf*

Plastics Europe / Mike Neal: *Document in ECB-I-18-06 16-02-11 - FC-143b.pdf*

Plastics Europe / Mike Neal: *ECB-I-18-06 16-02-11.pdf*