**Reviewer's report**

**Title:** Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances and childhood atopic dermatitis: a prospective birth cohort study

**Version:** 0 **Date:** 04 Sep 2017

**Reviewer:** Berit Granum

**Reviewer's report:**

The objective of the present study (ENHE-D-17-00244) was to examine the association between prenatal exposure to PFASs and childhood atopic dermatitis (AD) in children up to 2 years of age. Ten PFASs were analysed of which eight were included in the exposure-health association analyses. Adequate statistical analyses were performed. The authors conclude that prenatal exposure to PFOA, PFNA, PFDA, PFDoA and PFHxS significantly increased the risk of childhood AD in girls, but not in boys.

**General comments**

The study addresses a very relevant topic. Since the existing literature are conflicting making it difficult to draw any overall conclusion on the association between prenatal exposure to PFASs and allergy-related outcomes, more studies on this subject are needed. The discussion includes updated considerations on both epidemiologically and mechanistically issues. The manuscript is well-written, although some clarifications/modifications are needed (see specific comments). The correct abbreviation for perfluoroalkyl and polyfluoroalkyl substances is PFASs and not PFAS. Expect in instances such as e.g. PFAS levels, PFAS exposure.

**Specific comments**

**Abstract:**

The abstract stated that 811 children completed the 2-year follow-visit. However, since 124 of these do not have PFAS measurements, it should be stated clearer that exposure-health associations was performed on a study group of 687 children - not 811.

The PFASs mentioned in the conclusion of the abstract is not the same as in the conclusion of the discussion. PFDoA is not mentioned in the abstract's conclusion.
Introduction:

Page 4, 2nd section, lines 1-3: The authors mention several effects of PFASs such as immunotoxicity, hepatotoxicity and impaired thyroid function, but they end the sentence by writing mammary glands without any references to toxicity/functions of PFASs in these glands. Examples of effects on mammary glands should therefore be mentioned.

Page 4, 2nd section, lines 5-7: The authors should be more precise in how they cite these studies. The authors claim that in two epidemiologic studies, the exposure to PFASs was associated with asthma in adolescents, and then they refer to the studies by Dong et al. and Humblet et al. However, in Humblet, a positive association was found between PFOA and asthma, whereas there was a negative association between PFOS and asthma (and wheeze).

The authors should also add a reference for their last statement that no associations between PFASs and asthma were found in children up to 3 years of age.

Page 5, 1st section, lines 3-6: Delete atopic dermatitis at the end of the sentence in line 6.

Material and methods:

Statistical analyses on pages 8-9: The authors give a list of potential confounding factors. They should also add a description on the method used for choosing confounders to be included in the final adjusted statistical analyses (e.g. a priori selection, selection based on statistical significance, selection based on DAGs).

Results:

The number of children with AD is mentioned far down in the text. This information is important and should be mentioned early in the result section and not just listed together with the other population characteristics. The number of children with AD is shown in the column headings of table 1 without any percentage. Please add the percentage also in the table.

Information on maternal smoking and drinking during pregnancy are only mentioned in the text and not shown in Table 1. Please add these characteristics in Table 1.

Page 10, 1st section, line 8: The authors should specify that the passive smoking is due to paternal smoking as stated in table 1.
Page 11, 1st section: Please add a sentence stating that none of the other PFASs were significantly associated with AD.

Page 11, 2nd paragraph, lines 1-4 and Table 5: The authors state that PFOA, PFNA PFDA, PFDoA and PFHxS were significantly associated with AD in girls. In addition, the associations between AD and PFNA Q4 and PFDA Q4 are highlighted in bold figures, further indicating a statistically significant association. However, the 95% CI are 0.98-4.78 and 0.99-4.49, respectively. Since the CI crosses 1, this indicate that the findings are not statistically significant. The authors should change or moderate their statement regarding what associations are statistically significant.

Page 11, 1st section: The authors should add one sentence mentioning what PFAS-AD associations that are not statistically significant (e.g. for PFOS and PFBS).

Table 1:
Since the exposure-health analyses are performed on a population where n=687, you should consider adding a new column showing the figures for this population. Alternatively, deleting the n=811 and replace this by n=687.

Please add information in the table text that the figures in brackets are percentages.

Consider showing the percentages with only one decimal.

Table 2 and 3:
Are the analyses precise enough to give the PFAS concentrations with two decimals? The authors should consider reporting the concentrations with only one decimal.

Table 4 and 5:
In the footnote, confounding factors have been listed. Is this an overview over all the potential confounders or all the confounders included in the final statistical analyses? Please specify.

Table S1:
Since the exposure-health analyses are performed on a population where n=687, the authors should consider adding a new column showing the figures for this population. Alternatively, deleting the n=811 column and replace this by n=687.
Table S2:

Please add footnotes similar to Table 4 and 5.

Discussion:

Page 12, 1st section: This statement should be modified according the comments above on statistically significance and CI-intervals (Page 11, 2nd paragraph, lines 1-4 and Table 5).

Page 12, 3rd section, lines 2-4: I'm not sure the study be Anderson-Mahoney et al. is relevant to include in the discussion due to several risk-of-bias concerns. In the NTP Monograph (from September 2016) on PFOS and PFOA they concluded that "However, the study had a number of serious risk-of-bias concerns and was rated probably high for all three key risk of bias questions: (1) failure to consider most important confounders (e.g., smoking, body mass index, and socioeconomic status), (2) exposure characterization was based on residence in an area with drinking water contamination for at least one year with no information as to how variables such as percent of residents reporting water consumption were used, and (3) disease outcomes were obtained by questionnaire with no indication that the questionnaire had been validated (see Figure D34). In addition, the participants were plaintiffs or potential plaintiffs in a lawsuit regarding PFOA exposure of residents near a Teflon manufacturing plant on the Ohio River in West Virginia and therefore likely knew of their exposure and potential health effects." If the author still wants to include this study in their discussion, the bias questions from the NTP monograph should be addressed.

Page 12, 3rd section, lines 4-6: See comments above (Introduction, Page 4, 2nd section, lines 5-7). The authors need to be more precise when referring to the findings in other studies.

Page 14, 3rd section: The authors should include more discussion of strength and limitations in that this is an essential part of epidemiology.

Conclusion:

The conclusion should be modified according to the comments above (Page 11, 2nd paragraph, lines 1-4 and Table 5).
Level of interest
Please indicate how interesting you found the manuscript:

An article of importance in its field

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

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