

HBM-II values for perfluorooctanoic acid (PFOA) and perfluorooctane-sulfonic acid (PFOS) in blood plasma

Statement by the Human Biomonitoring Commission of the German Environment Agency

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For the evaluation of internal exposure to harmful substances, the Human Biomonitoring Commission of the German Environment Agency (HBM Commission) develops toxicologically justified assessment values (HBM-I and HBM-II values). The HBM-I value corresponds to the concentration of a substance in human biological material below which, according to the current status of assessment, no adverse health effects are to be expected. Consequently, no action is required if the HBM-I value is not exceeded [HBM Commission 1996]. In 2016, the HBM Commission developed HBM-I values of 2 ng PFOA/ml and 5 ng PFOS/ml in blood serum or plasma, respectively. A detailed delineation of supporting arguments was published in April 2018 [HBM Commission 2018]. In contrast to the HBM-I value, the HBM-II value corresponds to the concentration of a substance in human biological material which, when exceeded, may lead to health impairment which is considered as relevant to affected individuals [HBM Commission 1996, 2014].

HBM-II values for PFOA and PFOS

On 17th September 2019, the HBM Commission established the following HBM-II values:

Women at child-bearing age:

- 5 ng PFOA/ml blood plasma,
- 10 ng PFOS/ml blood plasma

All other population groups:

- 10 ng PFOA/ml blood plasma,
- 20 ng PFOS/ml blood plasma

Substantiation

The assessment was based on a systematic and continued review of the epidemiological and toxicological literature, together with an evaluation of data to determine points of departure for deriving the HBM-II values. As a result of this procedure, the evaluation focused on the following effects:

1. Reduced birth weights and developmental toxic effects,
2. Reduced fertility,

3. Reduced antibody formation,
4. Increased cholesterol concentrations (LDL and total),
5. Type II diabetes

Numerous other effects are described in the literature. For a synoptic review, the reader is referred to the document by the U.S. ATSDR (Agency for Toxic Substances and Disease Registry) [2018] which evaluates the reported data on different health endpoints in experimental and human studies, including mortality, body weight, respiratory, cardiovascular, gastrointestinal, haematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, developmental and other non-carcinogenic effects as well as cancer.

Following discussion in the HBM Commission, the effects listed above (1-5) were selected as relevant for the assessment. The discussion was based on an expert opinion, summarizing and evaluating the toxicological and epidemiological literature on these health impairments [Schümann et al. 2019]. The current PFOA/PFOS assessments by the U.S. ATSDR [2018], the European Food Safety Agency (EFSA) [2018] and other expert bodies are also included and discussed in this expert opinion. Existing uncertainties regarding the underlying mechanisms of action, their interactions and the problems of causal interpretation of associations are described on this occasion.

Methodology

Different methods were used to select points of departure (PODs) which, when exceeded, may lead to health impairment.

- Benchmark dose (BMD) modeling was selected to derive a POD for the HBM-II value, when appropriate.
- In cases where no suitable data could be selected for BMD analysis, a POD was derived by means of a population-related risk assessment provided adjusted regression analyses for examination of the dose/body burden-effect relation were available.
- In addition, quantile comparisons of the dose/body burden-effect relation were selected as POD for the HBM-II values. For this, the median of measured values in the lowest exposure quantile, showing a statistically significant effect and trend, was used as POD for the HBM-II value, whereas the lower limit of this quantile is used for determination of the HBM-I value.

Derivation of values

The methods for deriving the PODs for the HBM-II values for PFOA and PFOS are briefly described below. They were presented at several meetings of the HBM Commission and discussed with regard to existing uncertainties in the assessment.

1. Developmental toxicity and reduced birth weights

Developmental toxicity

In animal experiments, reduced litter and body weights, impaired weight development and reduced litter sizes are among the most frequently found effects after prenatal or perinatal exposure of mice and rats. Also, teratogenic effects on bone formation [Lau et al. 2006; Koskela et al. 2016; van Esterik et al. 2016] and impaired development of mammary glands [Macon et al. 2011; Tucker et al. 2015] were observed after low-dose exposure to PFOA. Furthermore, offspring of exposed dams showed changes in liver cells which became more apparent in the adult stage or developed in this late phase, long after the end of prenatal treatment [Filgo et al. 2015; Quist et al. 2015]. After exposure to PFOS during development, neurotoxic effects, such as astrogliosis in the cortex and hippocampus [Zeng et

al. 2011], behavioral changes [Butenhoff et al. 2009], effects on the glucose and lipid metabolism [Wan et al. 2012; Lv et al. 2013; Wan et al. 2014] as well as necrosis in the placenta and resorption of fetuses and stillbirths [Lee et al. 2015] were described, in addition to reduced birth weights [Luebker et al. 2005a; Luebker et al. 2005b]. Developmental toxicity was detected at very low doses and was among the most sensitive effects observed after PFOA treatment. While developmental toxicity was also described after exposure to PFOS, immunotoxic effects were the most sensitive effects after exposure to this compound.

Reduced birth weights

In a comprehensive meta-analysis of data on the relation between prenatal exposure to PFOA and birth weights as detected in experimental investigations in animals and epidemiological studies in humans [Johnson et al. 2014; Koustas et al. 2014], the authors found sufficient evidence of prenatal exposure to PFOA resulting in a reduction of foetal growth and, consequently, of birth weights. Human data showed stronger associations between PFOA concentrations in serum and birth weights, when body burden measurements were conducted during the second half of pregnancy. The results for PFOS were similar, although weaker with regard to potency. However, this may result in a comparable effect size in the general population, since higher average serum concentrations of PFOS are frequently determined. So far, no studies are available, including sufficiently large sample sizes to assess the risk for the criterion of birth weights < 2500 g. Based on the meta-analysis, a reduction of birth weights by approximately 20 g per ng PFOA/ml or 15–20 g per ng PFOS/ml has been described. A PFOA / PFOS-associated reduction in birth weight should not be of the order of magnitude of the effects of smoking during pregnancy [Vélez et al. 2015] and should not significantly increase the rate of births below 2500 g. The POD_{HBM-II} values chosen are about 10 ng PFOA/ml or 15 ng PFOS/ml.

2. Reduced fertility

Epidemiological studies relying on the indicators of time-to-pregnancy and infertility suggested an adverse association in studies covering higher PFOA/PFOS concentrations in serum. However, the relation was statistically significant in multiparae only. Taking into account the uncertainties resulting from limited toxicological and epidemiological information, the respective findings of suitable studies were included in the overall assessment [Fei et al. 2009; Whitworth et al. 2012b; Vélez et al. 2015]. The ranges suggested for POD_{HBM-II} are 3-10 ng PFOA/ml and 10-20 ng PFOS/ml.

3. Immune system - reduced antibody formation

Both, animal studies and epidemiological investigations in humans reported negative relations between exposure to particularly PFOS, but also to PFOA and humoral immunity. Moreover, the U.S. National Toxicology Program (NTP) [2016], ATSDR [2018] and EFSA [2018] concluded that immunotoxicity is a relevant endpoint for these compounds. Although a cohort study on humoral immunity after tetanus/diphtheria vaccination in children suggested $PODs$ at rather low internal exposure levels to PFOA and PFOS (< 10 ng/ml serum) [Grandjean et al. 2012; Grandjean and Budtz-Jørgensen 2013], human data from epidemiological studies were regarded as insufficient at present for deriving $HBM-II$ values. Reasons include the overall small number of studies, partially inconsistent results, and difficulties to extrapolate from the endpoint “antibody concentration” to risks of infectious diseases. Because of this, the POD for PFOS was developed on the basis of an experimental study on influenza virus-induced mortality in mice [Guruge et al. 2009]. Depending on the method of derivation, a POD_{HBM-II} between approximately 1 ng PFOS/ml ($BMDL_{10}$) and approximately 25 ng PFOS/ml (plasma concentration in the highest exposure group under consideration of a total assessment factor of 25) was calculated. For PFOA, the data situation is currently not considered sufficient to determine a POD_{HBM-II} .

4. Increased (LDL und total) cholesterol concentrations

Increased total and LDL cholesterol concentrations have been found to be associated with PFOA and PFOS body burdens in studies on workers, in highly exposed population groups, and also by general population studies. The concentration-effect function observed shows a steep increase in the lowest dose range already, and it seems to approach a horizontal asymptote at high concentrations [Steenland et al. 2009; Eriksen et al. 2013]. The PFOA/PFOS-associated rise in mean values correlates with a significant increase in the rate of values exceeding clinical LDL and total cholesterol reference ranges in the studies. In a population-related risk assessment, an increased risk of cardiovascular diseases for adults is seen, based on current literature. The resulting POD_{HBM-II} values are about 10 ng PFOA/ml and about 20 ng PFOS/ml.

5. Type II diabetes

Up to 2018, only small epidemiological studies with heterogeneous results had been available to assess a possible association with the incidence and prevalence of type II diabetes. This situation has changed considerably since the American Nurses' Health Study II [Sun et al. 2018] was published. In the prospective cohort study (initial survey of healthy females in 1995–2000, N= 116,430) with a long follow-up period (recording of 793 incident cases by 2011), and with a good quality assurance of diagnoses, the findings of an embedded case-control study have suggested a significant (odds ratio > 1.5 in the tertile comparison) incidence risk monotonically increasing with PFOA and PFOS serum concentrations. In the analyses, adjusting influencing factors were comprehensively included, and the stability of results was checked by means of sensitivity analyses. Against the background of a PFAS-associated increase of the incidence risk of gestational diabetes, which was also documented in literature, such aspects in the female population were included in the assessment. The data situation suggests opting for POD_{HBM-II} values of about 7 ng PFOA/ml and 8 ng PFOS/ml.

Assessment

Based on the associations derived from literature, the resulting points of departure for deriving HBM-II values for PFOA and PFOS are in the range of 1-30 ng PFOS/ml, and 3-10 ng PFOA/ml, respectively. It is within these ranges that the HBM Commission has established the HBM-II values mentioned above (10 ng PFOA/ml, 20 ng PFOS/ml).

For women of child-bearing age, the HBM-II values chosen are lower (5 ng PFOA/ml and 10 ng PFOS/ml), taking into account the indications of developmental toxic effects of these compounds and the findings of epidemiological studies in humans on associations between elevated PFOA/PFOS levels in the blood and reduced fertility, as well as indications of a PFAS-associated increase of the incidence of gestational diabetes and gestosis.

Discussion / Interpretation

To date, the modes of action underlying the associations between elevated PFOA or PFOS concentrations and adverse health effects have not yet been sufficiently understood. Both, the HBM-I and the HBM-II values for PFOA and PFOS are based on the assessment of the population-related risk of changes in the selected effect indicators. The POD_{HBM-II} values presented here are related to quantitatively defined changes (e.g. by 5-10 %, calculated with a confidence interval in a population) in certain target parameters (morbidity, laboratory values, among others) that are judged to be adverse. The results of the evaluation lie somewhat lower in the order of magnitude than the values resulting from EFSA's TDI derivations [EFSA 2018], which seems conditional by using other BMD methods, the gender differentiation, and by the uncertainties of toxicokinetic assumptions made by EFSA (including PFOA / PFOS distribution volumes).

The HBM-II values were chosen from the range of POD values by expert assessment, considering the uncertainties and the specifics of certain target groups. However, these values cannot be used to quantify, with sufficient certainty, an individual's risk of suffering health impairment as a result of her/his internal exposure to PFOA or PFOS. This is why the signal given by the current HBM-II value definition, that on principle immediate action to reduce exposure is needed and environmental medical care should be arranged for the person concerned, can only apply to a limited extent for the values stated above. The HBM Commission has been aware of this but nevertheless, wanted to provide points of reference for population-related measures by establishing these values. Both the definition and derivation of HBM values are intended to be discussed again in the next appointment period of the Commission.

To date, there are no clear findings that would provide evidence of a genotoxic mode of action of PFOA and PFOS [NTP 2019a, b]. Based on a recent chronic study in rats, the NTP concluded that there is "clear evidence of carcinogenic activity" of PFOA in male animals and "some evidence of carcinogenic activity" in female rats [NTP 2019c]. At the beginning of December 2019, after public comment, the results were discussed and professionally confirmed at an NTP expert hearing (peer review panel) [Sheena 2020].

In case of genotoxic carcinogens, no HBM values will be derived because there is no threshold of effects [HBM-Kommission 2014]. Against the background of limited indications of increased tumour incidences from a few epidemiological studies it is required to closely follow the development of scientific data, in particular with regard to tumour-promoting properties, to check whether re-assessment is required.

Measurement values exceeding the HBM-II value give reason for concern because health impairment may occur, in principle. However, health impairment does not have necessarily to result from such concentrations. Therefore, affected individuals should be offered environmental medical care or consultation, and, where appropriate, also long-term monitoring including follow-up measurements. Further exposure should be avoided immediately by eliminating specific sources of exposure, as far as these can be identified. Thus, the range of values exceeding the HBM-II value has to be regarded as a range requiring intervention (i.e. the HBM-II value has to be regarded as an intervention or action threshold level) [HBM Commission 2014]. If the HBM-II value is found to be exceeded in the context of first-time measurement of PFOA or PFOS concentrations in the blood, a control measurement should be carried out at first. Furthermore, it is recommended to identify and, if appropriate, consistently eliminate possible sources of PFOA/PFOS exposure of affected individuals. In addition to occupational sources of PFAS exposure, these may include, above all, the consumption of drinking water or food with elevated PFOA/PFOS levels (such as fish from contaminated waters), according to the current state of knowledge. Presently, the HBM Commission does not see any reason for recommending the determination of clinical-chemical parameters in cases where the HBM-II value is exceeded to a moderate extent, and other risk factors or pre-existing illness do not exist. No attempts should be made to accelerate the excretion of the compounds, PFOA or PFOS, because there is insufficient medical justification, and appropriate methods are missing.

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Compliance with ethical guidelines

Conflict of interest: There is no conflict of interest.

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