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Helsinki, 20 February 2019

Substance name: ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoate
EC number: 700-242-3
CAS number: 62037-80-3
Date of latest submission(s) considered[1]: 21 March 2018
Decision/annotation number: Please refer to the REACH-IT message which delivered this communication (in format SEV-D-XXXXXXXXXX-XX-XX/F)
Addressee(s): Registrant(s)[2] of ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoate (Registrant(s))

DECISION ON SUBSTANCE EVALUATION

Based on Article 46(1) of the REACH Regulation (Regulation (EC) No 1907/2006), ECHA requests you to submit the following information on the registered substance:

1. Carcinogenicity study in mice via oral route; test method OECD 451.

2. Human biomonitoring study in volunteering workers at the manufacturing site, as specified in Appendix 1.

You have to provide an update of the registration dossier(s) containing the requested information, including robust study summaries and, where relevant, an update of the chemical safety report by the deadlines as defined below:

Request 1: the information required according to point 1 above shall be generated and provided by **28 November 2022**.

Request 2: The information required according to point 2 above shall be generated and provided by **01 March 2021**.

In addition to the robust study summaries, you shall submit the full study report for test method OECD 451 by the same deadline.

The deadlines take into account the time that you may need to agree on which of the Registrant(s) will perform the required tests (3 months is allocated for this).

Appendices

The reasons of this decision and any further test specifications of the requirements are set out in Appendix 1. The procedural history is described in Appendix 2. Further information, observations and technical guidance as appropriate are provided in

[1] This decision is based on the registration dossier(s) at the end of the 12-month evaluation period.

[2] The terms registrant(s), dossier(s) or registration(s) are used throughout the decision, irrespective of the number of registrants addressed by the decision.

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Appendix 3. Appendix 4 contains a list of registration numbers for the addressees of this decision. This appendix is confidential and not included in the public version of this decision. Appendix 5 contains a summary of the physico-chemical properties, half-lives, toxicological profiles, and (self-)classifications of the registered substance and the related substance ammonium pentadecafluorooctanoate (APFO) and their ions.

Who performs the testing?

Based on Article 53 of the REACH Regulation, you are requested to inform ECHA who will carry out the study/ies on behalf of all registrant(s) within 90 days. Instructions on how to do this are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has a suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals

Authorised[3] by Christel Schilliger-Musset, Director of Hazard Assessment

[3] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

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Appendix 1: Reasons

Based on the evaluation of all relevant information submitted on the registered substance ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoate and other relevant available information, ECHA concludes that further information is required to enable the evaluating Member State Competent Authority (MSCA) to complete the evaluation of whether the substance constitutes a risk to human health and/or the environment.

The evaluating MSCA will subsequently review the information submitted by you and evaluate if further information should be requested to clarify the concern for carcinogenic potential in humans, bioaccumulation in humans (blood) and subsequent risks, and suspected PBT/vPvB in the follow up process.

The registered substance on the CoRAP is an ammonium salt, however under aqueous conditions (e.g. in blood or water), this substance will dissociate into ammonium ions, and 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoate ions "HFPO-DA" which are responsible for the observed effects.

The registered substance induced tumours in a two-year carcinogenicity study in rats. It cannot be excluded that these tumours are induced by a mode of action (MoA) other than peroxisome proliferator-activated receptor alpha (PPARα) activation and are therefore considered relevant for humans. A carcinogenicity study in mice is requested to further evaluate the carcinogenic potential of the registered substance and to determine if/which further action is needed, for example risk management measures to be taken.

The half-life of HFPO-DA in humans cannot be established based on the current data available. Consequently, the bioaccumulation potential of the registered substance in humans (blood) and subsequent risks are unknown. For PBT assessment, further information is needed to conclude whether or not HFPO-DA is bioaccumulative. Default parameters, such as log K_{ow} and BCF, are not suitable parameters for assessment of the bioaccumulation potential in this case. Therefore, information on the half-life of HFPO-DA in humans is needed to clarify the concerns relating to human health hazard and risk, and PBT properties.

It is noted that The Netherlands MSCA has prepared a regulatory management option analysis (RMOA) for the registered substance. Consultation with the MSCAs has taken place (consultation with the Registrant has taken place on an earlier draft in June - August 2018). This analysis proposes that one appropriate risk management option could be SVHC identification according to Article 57(f) of REACH due to the apparent toxicity, very high persistence, mobility, long range transport potential, exposure to humans and the environment and difficulty to remove the substance from the environment. Another considered regulatory risk management option is a proposal for harmonised classification for Carc. Cat 2. This process aimed at identifying the regulatory risk management that can already be considered necessary based on available data; it does not make the requests in this substance evaluation decision redundant since this substance evaluation decision addresses concerns of carcinogenicity which could lead to a more severe classification, and of the half-life in humans (bioaccumulation potential) which could lead to identification of the substance as PBT/vPvB and/or a different DNEL for workers; in addition, this decision indicates a concrete concern to be addressed, while the RMOA explores a possible need for further regulatory management options but does not involve any decision.

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1. Carcinogenic study in mice via oral route; test method OECD 451.

The concern(s) identified

The information in the registration dossier includes one carcinogenicity study performed in rats. In this study, tumours were induced upon exposure to the registered substance. However, the data are insufficient to fully elucidate the concern for human health. In this specific case the information on carcinogenicity does warrant further information to assess the classification (potential for Carc. 2 or Carc. 1B). Adequate classification is of importance for determining the need for follow-up regulatory action.

The registered substance (FRD-902) is used during industrial processing and the dossier shows exposure of workers to the registered substance. Furthermore, there is sufficient evidence of exposure of the general population to the anion of the registered substance via several routes including drinking water (Gebbink et al., 2017), local emitted air ([redacted], 2016a) and home grown fruits and vegetables ([redacted], 2018). Therefore, there is a potential risk for workers and the general population to be clarified.
In case of sufficient evidence for carcinogenicity, further regulatory action may be needed to guarantee safety of workers and the general population.

In addition, there is a potential risk for the environment and humans via the environment associated to persistence and bioaccumulation, and the requested data will also contribute to the PBT assessment. The registered substance is currently self-classified as STOT RE 2, based on hepatotoxic effects. However, the evidence for harmonised classification as STOT RE is borderline and therefore it is questionable whether the T criterion of PBT is fulfilled based on this endpoint. The current data for the registered substance are not sufficient to conclude whether classification for carcinogenicity is triggered, and to differentiate between a carcinogenicity classification in CLP Cat. 1B or Cat. 2. Harmonised classification for Carc. Cat. 1B may impact occupational exposures through the Carcinogens and Mutagens Directive (CMD). It will also make the registered substance a candidate for SVHC according to art. 57(a), be of influence for granting industrial emission permits under the Industrial Emissions Directive (IED) and will fulfil the T criterion for PBT identification according to Article 57(d) of REACH. The potential bioaccumulation is addressed by the request of a human biomonitoring study in this decision.

In comparison, harmonised classification for Carc. Cat. 2 will not trigger any regulatory risk management measures for workers nor any emission reduction under IED. It will not be sufficient to meet the criteria for SVHC under Article 57(a) and will not be sufficient to meet the T-criterion for PBT identification according to Article 57(d).

Why new information is needed

One carcinogenicity study with rats, treated with the registered substance, demonstrated statistically significant induction of adenomas/carcinomas in the pancreas in males, statistically significant induction of hepatocellular adenomas and carcinomas in females, and increased incidence of Leydig cell tumours in the testes (Rae et al., 2015). According to you, the Registrant, these tumours are not relevant to humans. This interpretation is mainly based on the MoA by which tumours are assumed to be induced, i.e. interaction via PPARα. According to you, HFPO-DA activates PPARα, resulting in toxicity and tumours in the liver, pancreas and testes of roents. You state that this mechanism is not expected to be relevant for species other than rats and mice, including humans, who seem to lack tumour induction upon treatment to PPARα agonists.

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However, when comparing the registered substance to perfluorooctanoic acid (PFOA), it is concluded that the tumours observed may be considered relevant for humans. Published reviews on the carcinogenicity of PFOA indicate that PFOA-induced carcinogenicity should be considered relevant for humans, because MoAs other than via PPARα cannot be excluded (US-EPA, 2016; EFSA, 2008; IARC, 2016).

The registered substance is used as a [redacted]. A comparison of the toxicological properties of both ammonium salts (the registered substance and APFO) is considered relevant. The substances have many similarities: both are ammonium salts of perfluoroalkyl acids (APFO is the ammonium salt of PFOA, a perfluorinated carboxylic acid; the registered substance is the ammonium salt of HFPO-DA, a perfluoroalkyl ether carboxylic acid) and in both cases the anion is the active substance. They show similarities in toxicological profiles. They show comparable effects in the liver and induce the same tumours, i.e. liver adenomas, Leydig cell adenomas and pancreatic cell tumours (Rae et al., 2015; Butenhoff et al., 2012; Biegel et al., 2001). Also the use in the production of [redacted] is similar.

PPARα is the most extensively studied signal pathway behind PFOA induced carcinogenicity, and it therefore is one of the primary suggested MoAs underlying the observed liver carcinogenicity in rats (US-EPA, 2016). However, studies report that PFOA may induce tumours via mechanisms other than PPARα in the liver, pancreas, and/or testes (Benninghoff et al., 2011; Benninghoff et al., 2012; Buhrke et al., 2015; Rosen et al., 2017; Cheng and Klaassen, 2008; Rosen et al., 2008; Ren et al., 2009; Abe et al., 2017; Scharmach et al., 2012). Furthermore, the link between PPARα, pancreatic acinar tumours and Leydig cell tumours remains uncertain (Klaunig et al., 2012). Also you indicate in the registration dossier that less definitive mechanistic data are available on the role of PPARα in the induction of pancreatic acinar cell tumours in rats, and mechanistic data on the MoA for induction of testicular interstitial cell tumours in rats by PPARα agonists is less robust. Consequently, it is insufficiently supported whether the MoAs underlying liver-, pancreatic acinar-, and Leydig cell tumour development are (exclusively, with respect to liver tumours) linked to PPARα, and therefore the responses at these sites are considered relevant to humans.

ECHA is aware that PPARα induction as a relevant mechanism underlying human carcinogenicity in the liver is under debate (Corton et al., 2017; Felter et al., 2018). It is known that the expression level of PPARα is about ten-fold lower in the human liver compared to that in rodents (Palmer et al., 1998). Additionally, PPARα-dependent mechanisms are illustrated to be less pronounced in non-human primates (Hoivik et al., 2004). However, RAC still concluded in 2011 that contribution to PFOA-induced liver tumours of molecular pathways other than PPARα cannot be fully excluded (ECHA, 2011). That is to say, it is doubted whether PPARα is the only MoA by which PFOA may cause liver cancer. PFOA demonstrated to induce liver toxicity in monkeys and in PPARα knockout mice under a subchronic and acute exposure regimen respectively (Butenhoff et al., 2002; Wolf et al., 2008). This illustrates that liver toxicity is not induced via PPARα activation solely.

Gene expression patterns of PPARα knockout mice treated with PFOA, PFOS, PFHxS and PFNA showed that about 11-24% of the regulated genes activated by PFASs act in a PPARα-independent manner (Rosen et al., 2008; Rosen et al., 2017). In comparison, only 6% of the genes activated by the PPARα agonist DEHP (di(2-ethylhexyl) phthalate) were independent of PPARα regulation, and for the PPARα agonist WY-14,643 this was only 2% (Ren et al., 2010; Rosen et al., 2017). Thus, among PPARα agonists, there is

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difference in how many, and the degree by which they are able to activate PPARα-independent genes. This complicates comparison of biological effects induced by chemicals that are known to activate PPARα, such as fibrates, phthalate esters, and per- and polyfluorinated substances (PFASs).

Alternative mechanisms have been suggested by which PFASs could induce liver cancer. Studies have shown that PFASs affect the estrogen receptor ERα (Benninghoff et al., 2011, Benninghoff et al., 2012; Buhrke et al., 2015; Rosen et al., 2017), that PFOA activates PPARγ, constitutive androstane receptor (CAR), and pregnane X receptor (PXR) (Cheng and Klaassen, 2008; Rosen et al., 2008; Ren et al., 2009; Abe et al., 2017), and that PFOA inhibits the function of hepatocyte nuclear factor 4α (HNF4α) (Scharmach et al., 2012). These findings indicate that tumour formation upon exposure to PFOA via other MoAs than PPARα cannot be excluded, and a similar conclusion might hold true for HFPO-DA. Therefore, the formation of liver tumours upon exposure to the registered substance in the rat should be considered relevant for humans.

For PFOA as well as HFPO-DA, the mechanism behind the induced pancreatic acinar cell tumours is not understood, and available data are limited. A proposed MoA involves activation of PPARα in the liver causing decreased bile acid flow and/or altered bile acid composition, which subsequently would result increased serum levels of the growth factor cholecystokinin (CCK, cholecystokinin-33 in humans), causing acinar cell proliferation with development of acinar cell tumours as a result (Klaunig et al., 2012). However, altered testosterone and estradiol levels, CCK expression, CCKA receptor overexpression, and a high fat diet are also mentioned as factors having impact on the pancreatic acinar cell hypertrophy, hyperplasia, and tumours observed in the rat. Data supporting this MoA for PFOA remain confined to the observations that PFOA increased biliary excretion (Minata et al., 2010) and altered expression of bile transporters (OATPs and MRPs) in mice (Cheng and Klaassen, 2008; Maher et al., 2008). For HFPO-DA, no data underlying the MoA for pancreatic acinar cell tumours are available. The limitations in available data on the mechanism(s) underlying the pancreatic acinar cell tumours preclude any conclusion concerning the interspecies differences for the observed pancreatic acinar cell tumours induced by the registered substance, and therefore the observations should be considered relevant for humans.

Also the link between PPARα and Leydig cell tumours remains uncertain (Klaunig et al., 2012), but the modulation of testosterone levels is suggested to play an important role in promotion of cell proliferation and testicular Leydig cell tumour development (ECHA, 2011; Klaunig et al., 2012; Sun et al., 2018). Studies have shown that PFASs affect the estrogen receptor ERα (Benninghoff et al., 2011; Benninghoff et al., 2012; Buhrke et al., 2015; Rosen et al., 2017), and reported that increases in testicular interstitial fluid estradiol and TGFα as well as affected Leydig cell functioning potentially contribute to Leydig cell adenomas (Biegel et al., 1995). These results suggest a hormone interference MoA for PFOA, based on potential effects of steroid hormone synthesis. Based on the given, exposure to the registered substance could lead to testicular cancer via a non-PPARα related mechanism, and therefore Leydig cell tumour development observed in rats should be considered relevant to the human situation.

In conclusion, beyond the question on whether the biological responses observed in rodents related to the activation of PPARα are relevant to assess the carcinogenic potential in humans, contribution of other pathways to tumour development after exposure to the registered substance cannot be ruled out. Consequently, it is not certain whether PPARα is required for tumorigenesis in either rodents or humans, and therefore relevance of the tumour formation in humans cannot be excluded.

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Further, it is noted that carcinogenicity data for PFOA, classified as Carc. Cat. 2 under CLP, were available for the rat only. From kinetic studies with PFOA and HFPO-DA, it can be concluded that these substances show higher bioaccumulative potential in the mouse compared to the rat (Lau et al., 2007; Gannon et al., 2016). Additionally, from the registration dossier can be concluded that overall, the registered substance shows a higher toxic potency in mice compared to rats. Consequently, there is a lack of data with regard to the carcinogenic potential of these substances in species other than the rat, and therefore the requested carcinogenicity study in mice is warranted.

The current data are not sufficient to conclude whether classification for carcinogenicity is triggered, and to differentiate between a carcinogenicity classification in CLP Category 1B or Category 2. Therefore, further data are needed which will add to the weight of evidence for carcinogenicity.

What is the possible regulatory outcome

Together with the available results from the carcinogenicity study in rats, the information requested is needed for a full assessment to determine the adequate harmonised classification and labelling for carcinogenicity. The outcome will determine if further risk management measures are needed, as described above.

Considerations on the test method and testing strategy

To determine the level of concern and the subsequent consideration of the adequate classification of the substance (Carc. 1B, or 2), and follow-up risk management measures, a carcinogenicity study in a second species shall be performed. The study needs to be performed in mice; a carcinogenicity study with rats is already available. The study shall be performed according to OECD test guideline 451, using dose levels adequate to detect carcinogenic effects, but excluding excessive general toxicity.

You shall submit the full study report for the information requirement 1. Considering the complexity of the study requested, a complete rationale and access to all information available in the full study report (implemented method, raw data collected, interpretations and calculations, consideration of uncertainties, argumentation, etc.) are needed. This will allow the evaluating MSCA to fully assess the provided information, including the statistical analysis, and to efficiently clarify the concern for carcinogenicity.

Consideration of alternative approaches

For determining the carcinogenicity of a substance, the cancer bioassay is the only study available. A study according to OECD 451 is preferred, because the focus is primarily on carcinogenicity and not chronic toxicity. An OECD 451 study will be sufficient. The doses shall be set based on the results from the subchronic 90 day study and the current knowledge about the toxicokinetics in mice. Dose level setting shall aim to induce systemic toxicity at the highest dose level. In view of the difference in sensitivity between the sexes, higher dose levels for females shall be considered. Studies with shorter duration than the cancer bioassay may not provide sufficient time to develop tumours or toxicity by the registered substance.

The available in vitro and in vivo genetic toxicity and mutagenicity studies show that the registered substance is not genotoxic. In addition, EFSA concluded that the substance is non-genotoxic based on the same data set (EFSA, 2009). Further genotoxicity testing is not considered relevant.

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Studies of PFOA using humanised PPARα and knockout animals have demonstrated induction of adverse effects, indicating the likelihood of involvement of PPARα-independent mechanisms. In view of the similarities between PFOA and the registered substance, it is considered possible that the registered substance will also act via a PPARα-independent mechanism. On basis hereof, and with regard to the ethical use of animals, it is not requested to repeat the studies in PPARα knockout animals and humanised PPARα but to conduct a carcinogenicity study in another species to further examine the carcinogenic potential of the registered substance and, if applicable, allow further risk management measures on basis of the carcinogenic potential of the substance.

Consideration of your comments on the draft decision and proposals for amendment (PfAs) and comments on PfAs

All comments provided by you have been taken into consideration and have been incorporated in the text where deemed appropriate.

Rather than taking into account available data on PFOA, your request was to focus on the registered substance itself. Therefore, the text was amended to specifically indicate the lack of information concerning the carcinogenic potential and the biological half-life of HFPO-DA in humans.

You commented that sufficient data are available for the registered substance to conclude that the observed tumours are PPARα-related. Humans are refractory (and rodents are susceptible) to liver carcinogenesis following exposure to PPARα activators, and therefore the tumorigenic responses in rodents are not reflective of the human experience. According to you this is indicated, among other things, by the lack of hepatocarcinogenicity after therapeutic administration with the PPARα activators ciprofibrate and fenofibrate in humans. Consequently, according to you, there is no basis for carcinogenicity concern in humans and no credible basis for classification as a human carcinogen under the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) or CLP. ECHA does not agree that there is a lack of concern for carcinogenicity of the registered substance, and stipulates that comparison between PPARα activators should be done with caution. Based on the data available for the registered substance, it is not certain whether PPARα is exclusively responsible for the observed tumorigenesis in rats. The text was amended to further justify this, taking into account your comments.

You also commented that protection from adverse liver toxicity would protect against cancer, when taking into account the NOAEL of 1 mg/kg bw/day. It must be stated that the carcinogenicity study in mice is requested to evaluate the intrinsic properties of the registered substance essential for further risk management measures. From kinetic studies with PFOA and HFPO-DA can be concluded that these PFASs show higher bioaccumulative potential in the mouse compared to the rat (Lau et al., 2007; Gannon et al., 2016). Consequently, this may affect the point of departure used for derivation of the DNEL. Due to the current lack of information on the half-life of the registered substance in humans, an assessment factor of 66 for potential kinetic differences (as established for PFOA) needs to be applied in the derivation of the DNELs for the registered substance, to account for the potentially large interspecies differences. When using a point of departure of 0.1 mg/kg bw/day, and applying the additional factor for potential kinetic difference of 66 and the factor for the interspecies remaining difference of 1.8, the worker DNEL for inhalation will be a factor 467 lower than the DNELs as derived by the Registrant ([redacted], 2016a). For several exposure scenarios, this results in

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risk characterisation ratios >1 (in the range 10-100), indicating a potential risk for workers. Should the outcome demonstrate that there is sufficient evidence for carcinogenicity, further regulatory action may be needed to guarantee safety of workers and the general population, as indicated above in the text.

You furthermore noted that the OECD 451 test is a descriptive toxicology test and it is not designed to, and will not, elucidate the rodent carcinogenicity mechanisms. Additionally, you argued that the required test is not considered appropriate with regard to the ethical use of animals. As discussed above, there is a concern which justifies testing under substance evaluation. The study is requested to investigate the carcinogenic potential of the registered substance. The requested study is intended to keep the number of required animals to a minimum to address the concern. As discussed above, alternatives or further examination of the mechanism would not be appropriate as several MoAs may be involved and need to be investigated, and the tumorigenesis involves multiple organs (not only liver). Hence, further examination of the mechanism would require even more testing and use of more animals, which is considered not proportionate.

In your comments you recommended engaging with toxicology experts from the Society of Toxicology (SOT) meeting held in San Antonio, Texas, in March 2018. We have reviewed the outcome of the SOT meeting. The abstracts however did not bring new data to address the concern in the Decision. It therefore did not change our view and requests in the Decision of the substance evaluation. Based on the evaluation of all information submitted on the registered substance by you and other relevant information available, ECHA still requests a carcinogenicity study in mice via oral route (test method OECD 451) and a human biomonitoring study in workers at the manufacturing site (as specified below) to evaluate whether the substance constitutes a risk to human health and/or the environment.

After circulation of the draft decision to MSCAs and ECHA, several PfAs were submitted. One MSCA commented that recently the wording of the dose level setting in carcinogenicity studies was changed in the OECD test guideline (OECD TG 451, July 2018), and this should be reflected in the text of this draft decision as well. You did not agree with this PfA, and noted that "it is unlikely that dosing can be such to produce tumours without overt toxicity from the very high doses associated with rodent tumours." The dosing in the 90 day subchronic toxicity study in mice however only showed some liver toxicity at the highest dose, and therefore based on extrapolation we expect these dosages should provide results without causing excessive toxicity. The proposal for amendment was accepted and the text was modified accordingly.

Another PfA was provided noting that additional arguments and references were included in the draft decision to further elucidate risk management measures after potential harmonised classification as Carc. Cat. 1B and to describe potential modes of action for carcinogenicity other than PPARα induction. You responded that the registered substance is not used in consumer products, that there is no risk for workers based on the current exposure, and the current permit emission levels for the registered substance are already low and you aim to reduce these emissions even further in the recent future. Furthermore, you stipulated that according to you, the biological effects observed in the liver are consistent with PPARα activation and are of limited relevance to humans. As addressed before, current uses and exposure indicate a potential risk. The carcinogenicity study in mice is requested to evaluate the intrinsic properties of the substance and for classification, which are essential for further risk management measures. The mode(s) of action for tumorigenesis of the substance are not elucidated.

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The third PfA was submitted by an MSCA, who proposed to remove the request for a second carcinogenicity study, or, in the event that the request for the carcinogenicity study remains, to revise the text. The MSCA was of the opinion that the concern for carcinogenicity does not justify the use of animals, and that another study would not lead to a change or improvement in risk management options. The study in rats showed effects which, according to this MSCA, are applicable for harmonised classification as Carc. Cat. 2, without any residual concern for carcinogenicity (the same results are expected in mice, based on the known biological response to PPARα agonists). Additionally, this MSCA had a divergent opinion with respect to the analysis and interpretation of the carcinogenic response observed in Rae et al. (2015). You agreed with this PfA and agreed with the provided arguments. Additionally, you provided your interpretation of the liver lesions observed in (sub)chronic rodent studies and your view on a lack of relevance for humans.

The MSCA furthermore indicated that the substance is only used under controlled conditions in an occupational setting, and exposure levels are estimated to be very low. You acknowledge this in your comments to the PfAs. Based on this, and the fact that the registered substance is non-genotoxic, the MSCA concluded that "the current DNEL (for workers) will be protective for any potential carcinogenicity concerns". With regard to exposure of the general population via drinking water, local emitted air, and homegrown fruits and vegetables, the MSCA proposed a back calculation to estimate the exposure and compare this to a general population DNEL, to estimate the risk and suggested to combine this with a mode of action analysis. They noted this should be done first, to assess whether there actually is a concern, before requesting a carcinogenicity study.

ECHA considers the carcinogenic effects (statistically significant induction of adenoma/carcinoma in the pancreas in males, statistically significant induction of hepatocellular adenomas and carcinomas in females, and increased incidence of Leydig cell tumours in the testes) observed in Rae et al. (2015) treatment-related. The combination of pancreatic acinar adenomas and carcinomas is considered justified. Furthermore, although the incidence of Leydig cell tumours in the highest dose group was not statistically significant, the incidence was out of the historical control range and therefore considered biologically relevant. Hence, these effects should be used to assess the carcinogenic potential of the registered substance as currently presented.

Based on the available data and in line with PFOA, it is not justified to attribute the observed effects in the carcinogenicity study by Rae et al. (2015) solely to PPARα. Further, carcinogenicity data for PFOA, as well as for the registered substance, is currently available for the rat only. Both substances show higher bioaccumulative potential in mice compared to rats (Lau et al., 2007; Gannon et al., 2016). Additionally, from the registration dossier can be concluded that overall, the substance shows a higher toxic potency in mice compared to rats. Consequently, there is a lack of information with regard to the carcinogenic potential of these substances in species other than the rat. A new OECD 451 study in mice with the registered substance will therefore provide new relevant information, which could potentially lead to harmonised classification as Cat. Carc. 1B and subsequent risk management measures. Decision-making on the appropriate classification is done by the RAC.

It can be concluded that HFPO-DA shows higher bioaccumulative potential in the mouse compared to the rat (Gannon et al., 2016). Additionally, from the registration dossier can be concluded that overall, the registered substance shows a higher toxic potency in mice compared to rats. Consequently, there is a lack of data with regard to the carcinogenic potential of these substances in species other than the rat. Given

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uncertainties, the existing evidence from this single carcinogenicity study is not sufficient to perform a robust quantitative assessment, as a study in mice could lead to a lower point of departure for carcinogenicity effects. Further issues on the derivation of the DNEL and RCRs are addressed below in request 2 and the option for mode of action analysis is addressed in the section on alternative approaches.

There is evidence of exposure of the general population to the registered substance via several routes ([redacted], 2016a; Gebbink et al., 2017; [redacted], 2017, [redacted], 2018). Although the individual exposures do not exceed the threshold values, (local) populations can be exposed via multiple exposure routes. Therefore, it was adviced for owners of a vegetable garden in close vicinity of the factory to limit the consumption of home grown vegetables and fruits ([redacted], 2018). Further, the registered substance belongs to the group of perfluorinated substances and resembles the toxicological properties of short chain perfluorinated carboxylic acids (PFCAs) and perfluorinated sulfonic acids (PFSAs). These combined exposures give rise to concern for the general population. Furthermore, the substance shows high persistency and its environmental concentration is expected to increase. Based on the above, ECHA did not agree to remove the request, however the proposed revisions were taken into account as described below.

In the case the request for a second carcinogenicity study would not be removed, the MSCA proposed several changes in the text of the draft decision, e.g. to elucidate the similarities between PFOA and the registered substance in terms of kinetics, physico-chemical properties, and toxicological profiles. The evaluating MSCA agreed with the proposed revisions, which further clarify the request. The draft decision was modified by providing further detail with respect to differences in bioaccumulation of the registered substance within various species. Furthermore, in Appendix 5, a summary of the physico-chemical properties, half-lives, toxicological profiles, and (self-) classifications of APFO/PFOA and FRD-902/HFPO-DA were provided. You agreed with the MSCA's proposals, but specified that structural/spacial differences between PFOA and HFPO-DA should be noted in this comparison as well, and their relation to the half-life and toxicity of the substance (e.g. assumed variation in efficacy to bind to organic anion transporters (OATs)). Last, you did not agree with the DNEL derivation as performed by the evaluating MSCA. As noted in request 2, you did not provide any data that support your hypothesis with regard to differences in OAT binding efficacy between PFOA and HFPO-DA and hence it remains unclear whether resorption of HFPO-DA in the lumen of the kidney will occur or not.

Conclusion

Based on the substance evaluation and in accordance with Article 46(1) of the REACH Regulation, ECHA concludes that you are required to carry out the following study using the registered substance subject to this decision:

> Carcinogenicity study in mice via oral route; test method OECD 451, using dose levels adequate to detect carcinogenic effects, but excluding excessive toxicity.

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2. Human biomonitoring study in volunteering workers at the manufacturing site.

The concern(s) identified

There is concern that the anion of the registered substance bioaccumulates in humans and poses a risk to workers and the general population. Further, there is concern that the substance may be PBT due to bioaccumulation in air breathing organisms which cannot be measured by bioaccumulation studies in aquatic organisms.

The registered substance has [redacted] PFOA [redacted]. PFOA is known to have a relatively long half-life in humans, i.e. 3.8 years (Olsen et al., 2007). This half-life is much higher than would be expected based solely on data from rodents and monkeys, in which half-lives of 2-4 hours up to 32.6 days were determined (Lau et al. 2007; Butenhoff et al., 2002). The half-life of HFPO-DA in rats is 0.2-3.6 h (alpha phase) and 23-89 h (beta phase), in mice it is 4.6-5.8 h (alpha phase) and 24-37 h (beta phase), and in monkeys it is 1.9-2.3 h (alpha phase) and 64-80 h (beta phase) (Gannon et al., 2016). However, the half-life of HFPO-DA in humans is unknown.

Observations with perfluoralkyl acids show chain length dependent binding to proteins and this chain length dependent affinity varies between proteins. Protein-binding may lead to slower elimination and result in a long half-life in human blood. Liver and blood and thus protein-rich compartments are important for the accumulation of perfluoroalkyl acids (Ng and Hungerbühler, 2014).

The registered substance has several similarities with APFO. They are both ammonium salts of perfluoroalkyl acids showing high persistency, and show similarities in toxic profile with the same assumed mode(s) of action. Based on these similarities, the measured kinetics of the registered substance in rodents and monkeys may underestimate the human situation. Toxicokinetics data of HFPO-DA indicate that the clearance time of the registered substance is lower compared to PFOA, which would suggest that the substance bioaccumulates to a lesser extent. However, a large difference in clearance time between animals and humans observed for PFOA may also be the case for HFPO-DA. Therefore, it is not possible to draw conclusions on the human clearance rate for HFPO-DA.

Recently, you provided data on HFPO-DA levels in the blood of workers ([redacted], 2017). Concentrations of HFPO-DA were found to be in the range of <0.001 – 0.2 µg/ml in human blood plasma. You indicated that workers at the plant site had been using HFPO-DA for approximately three years, and if this substance had biopersistence properties like PFOA, the blood levels would be expected in the range of 1 ppm (1 µg/ml). According to you, the results clearly showed that HFPO-DA levels were very low and not indicative of a substance with slow bioelimination. However these data provide insight into the exposure to HFPO-DA at one specific time point, they do not suffice in providing insight into the absolute value for the clearance time of HFPO-DA in humans. As only one measuring point is provided per study participant, no half-life can be established. Therefore, you are requested to perform a human biomonitoring study collecting two blood samples over a longer period of time.

Only information on the half-life of HFPO-DA in humans can demonstrate if the difference in half-lives between humans and rodents is indeed comparable to PFOA. Besides that, in this case the half-life in humans in itself is essential in the weight of evidence approach

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to determine if the registered substance is bioaccumulative (B) or very bioaccumulative (vB) according to REACH Annex XIII.

As long as the concern remains, an additional toxicokinetic assessment factor needs to be applied when deriving a DNEL to take into account the potential difference between kinetics in rodents and kinetics in humans. Due to the current lack of information on the half-life of HFPO-DA in humans, this additional toxicokinetic assessment factor is based on information of PFOA and is determined to be 66 ([redacted], 2016a). Taking this additional assessment factor into account, this results in a lower DNEL than is currently derived by you in the registration dossier. This revised DNEL results in RCRs for workers above 1. Therefore, based on the available data on hazard, kinetics and exposure, there is a concern regarding the risk of humans exposed to the registered substance.

Further, based on the findings and data for the registered substance and structurally similar perfluoralkyl carboxylic acids, further information is needed to conclude whether or not the substance is bioaccumulative. One OECD 305 study is available. However, based on information available for the structurally similar perfluoralkyl carboxylic acids, bioconcentration values in gill breathing organisms are not the most relevant endpoint to consider. Studies on PFOA show that there is a low bioaccumulation potential in fish but elevated levels of PFOA in human blood and a half-life in humans of 2-4 years (ECHA, 2013). PFOA was identified as being bioaccumulative based on a weight of evidence including the long half-lives in human blood, and a similar conclusion might hold true for the registered substance. In conclusion, the substance might be a PBT or vPvB substance but further information on its bioaccumulation potential is needed.

Why new information is needed

There is a concern that HFPO-DA bioaccumulates in humans and poses a risk to workers and the general population. There is a concern that the substance may be PBT due to bioaccumulation in air breathing organisms via mechanisms (such as protein binding) which cannot be measured by bioaccumulation studies in aquatic organisms. The registered substance is structurally similar to other perfluorinated chemicals and a similar bioaccumulation pattern compared to PFOA might occur. Therefore, it is plausible that the half-life of HFPO-DA in humans may be much higher than would be expected based on animal data, as demonstrated for PFOA.

Information on the half-life of HFPO-DA in humans may indicate a lower half-life in humans as compared to PFOA and may clarify the concern on a risk for human health. Due to a lack of information, assumptions are made based on information of PFOA. This results in a high assessment factor to take into account potential large interspecies differences. Information on the half-life of HFPO-DA in humans is needed to estimate the interspecies difference and apply a more precise assessment factor for the derivation of the DNEL. This may clarify the potential risks for human health.

Further, standard parameters such as log K_{ow} and BCF are not appropriate to assess the bioaccumulation potential of per- and polyfluoroalkyl substances. A human biomonitoring study is necessary to provide more information on the bioaccumulation potential of HFPO-DA.

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What is the possible regulatory outcome

Based on the outcome of the study, the half-life of HFPO-DA in humans canbe determined. This half-life can be compared to the values for rodents and be taken into account to determine the assessment factor for interspecies differences.

In case the interspecies difference is large and results in an RCR value of >1, further action such as risk management measures (RMMs) will be needed. Furthermore, if the weight of evidence shows that the registered substance meets the PBT or vPvB criteria or an equivalent level of concern, it will allow authorities to consider further regulatory risk management, e.g. identification as a substance of very high concern.

Considerations on the test method and testing strategy

Biomonitoring shall be carried out on volunteering workers from a manufacturing site of the Registrant located in the EU, where the substance is used in the production process and where exposure of workers is likely to occur. Information on these workers shall be gathered and listed, including gender, age, length of employment, working activities, and lifestyle. Further, detailed information on the exposure concentrations of each participant at the corresponding workplace in the manufacturing site is required. The study results shall be anonymised before inclusion in the registration dossier.

Determination of the half-life shall be performed according to the procedure stated below.

Blood shall be collected at two time points: 1) Friday, at the end of the work shift, but preferably several hours after the last potential exposure, and 2) Monday, before the start of the work shift. The participants shall not have worked at the manufacturing site during this weekend.[4] The number of participants shall be sufficient to cover interindividual variability, and be enough to determine a robust half-life of the registered substance. For this it is required that a sufficient number of participants are monitored to obtain two consecutive plasma concentrations that are above the limit of quantification (LOQ), to be able to calculate a half-life. The remaining number of participants that have quantifiable plasma concentrations after the period of around 60 h should be enough to calculate a standard deviation that reflects the variability between individual workers. During the recruitment of the participants, workers with the highest assumed exposure are preferred, e.g. workers involved in PROCs with the highest exposure estimates. Based on these measurements, the half-life of the registered substance must be estimated, assuming first order elimination kinetics. If the decrease is less than 20% over the period of around 60 h (assuming that a decrease of less than 20% cannot be demonstrated with sufficient reliability), further measurements may be requested in a follow-up substance evaluation decision, according to Article 46(3) of REACH, to be able to determine the half-life of the registered substance sufficiently.

For blood sampling and the bioanalytical measurements, the design and guidelines as used previously by the Registrant(s) and described in their report 'Determination of HFPO-DA in EDTA Human Plasma Samples' shall be used. Biomonitoring must be carried out in accordance with applicable national requirements.

[4] Or, in case of a deviating working schedule, blood shall be collected at two time points with a similar time interval.

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Notes for consideration

In order to prevent unnecessary testing of volunteers, you may consider to follow a tiered approach as outlined below:

1. Before the first sampling date: If there are more than five volunteers willing to participate, consider staggered inclusion of all volunteers, starting with five individuals involved in the PROCs with the highest exposure.

2. Before the second sampling date: If feasible, analyse the plasma of the first sampling before starting the second sampling and proceed only with those volunteers with quantifiable plasma concentrations above the LOQ.

3. After the second sampling date: If three or more volunteers have plasma concentrations sufficient to determine a robust half-life you may consider to terminate the study. Considering the potential variability in analysis, you may consider to reanalyse the plasma of the first sampling date together with the analysis of the plasma of the second sampling date.

4. If there are less than three volunteers that provide a robust half-life, the study should be continued with staggered inclusion of five additional volunteers when available, and follow the three steps mentioned above. You may consider to sampling volunteers to a maximum of 20, after which you could terminate the study irrespectively of the number of half-lives obtained.

Consideration of alternative approaches

There are no alternative approaches available. Considering the concern, the lack of testing alternative and, in particular the right to integrity under Article 3 of the Charter of Fundamental Rights of the European Union, biomonitoring on volunteered workers appears justified and proportionate.

When comparing the substance with PFOA and the interspecies differences observed for that substance are applied, risks are not controlled. Only information on the half-life of the registered substance in humans can demonstrate if the difference in half-lives between humans and rodents is indeed comparable to PFOA. Besides that, in this case the half-life in humans in itself is essential in the weight of evidence approach to determine if the registered substance is B or vB.

As previously indicated, observations with perfluoralkyl acids show a chain length dependent binding to plasma proteins in general. This protein binding contributes to the persistence of PFOA in the blood. Liver and blood and thus protein-rich compartments are important for the accumulation of perfluoroalkyl acids (Ng and Hungerbühler, 2014). The measurement of protein binding as an indirect manner to estimate the accumulation of the registered substance was considered but is not straight forward. Protein binding studies can elucidate bioaccumulation mechanistically to some extent. However, to extrapolate in order to conclude on bioaccumulation is uncertain. Means to extrapolate and interpret protein binding in regard to bioaccumulation are lacking and the mechanism of accumulation is not fully understood. Thus, it was not considered feasible to request a protein binding assay.

As bioaccumulation of perfluoralkyl acids is specific for liver and blood, less invasive sampling such as urine sampling is not suitable for determining the half-life of HFPO-DA.

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Consideration of your comments on the draft decision and PfAs, and comments on PfAs

It is argued that the half-life of PFOA is longer in humans compared to other species, since in humans there could be stronger reabsorption from the lumen of the kidney back into the blood by OATs (Yang et al, 2010). In your comments you indicate that HFPO-DA may very well be a poorer substrate for the OATs in the lumen of the kidney, since there are structural differences between PFOA and the registered substance. This is not further justified by the data you provided, and hence remains unclear. It is therefore not known what effect HFPO-DA has on the functioning of the OATs and if resorption of HFPO-DA in the lumen of the kidney will occur in humans or not.

In your comments you stated that the required study is personally invasive, is not reasonable given the use of volunteers, is not within the time- or quality control of the Registrant, and is not executable as described in the draft decision. ECHA does not agree and considers the request justified and proportionate. The request is necessary to address a concern related to worker exposure, is the least invasive measure, clearly indicates that biomonitoring shall be carried out on volunteering workers, and no alternative is available (see above).

ECHA clarifies that you are required to plan, arrange and set up the requested human biomonitoring study in workers at the manufacturing site and report on the outcome. You indicate concern that you have no control over potential exposure outside the workplace and noncompliance with your industrial hygiene practices. You also indicate your concern with relying on volunteers to show up at the scheduled time for blood drawing, as you experienced during a previous study that not all workers were present at the scheduled time. Therefore, you need to provide the exact time interval between the two measuring points, and should ensure the workers are not exposed to the registered substance at the workplace in between these times. Exposure outside the workplace is not expected to contribute significantly to the concentrations in the plasma over the study period of 60 hours. Since the study relies on the voluntary co-operation of workers, ECHA acknowledges it is not fully in your power to ensure sufficient measured data are provided. In the event that workers do not cooperate or if you are unable to provide sufficient measured data, you should document your efforts to undertake the requested study. In case of remaining uncertainties, the evaluating MSCA may have to make reasonable worst-case assumptions to address the concern. However, you have conducted a biomonitoring study with workers in 2017, indicating the feasibility of gathering such information and showing the willingness of workers to cooperate.

After circulation of the draft decision to MSCAs and ECHA, four PfAs were submitted, of which three focussed on the request for a human biomonitoring study in volunteering workers at the manufacturing site. A PfA was submitted proposing to consider modifications to the test method and testing strategy, to bring to the attention potential confounding exposure factors in the study, and to stress the evaluating MSCA has to make reasonable worst-case assumptions when the concern for bioaccumulation of HFPO-DA in humans cannot be withdrawn. You did not agree with this PfA. You commented that worker exposure is low, and the DNEL derived in the registration dossier is sufficiently low to protect against potential carcinogenic effects in workers. You indicated that conducting the human biomonitoring study in workers is invasive and will not lead to improved worker safety or allow for more refined risk assessment. Additionally, you indicated that there is no evidence of significant or widespread occurence of HFPO-DA in the blood of workers, based on the data you provided ([redacted], 2017). You furthermore indicated that the chance of successful derivation of

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a human half-life by conducting this study would be low. As noted above, RCRs as calculated by the evaluating MSCA are in the range of 10-100 and therefore workers could potentially not be protected against tumour development. We have a concern that your DNEL is not protective enough for potential bioaccumulation in humans. You already illustrated that it is feasible to conduct a human biomonitoring study in volunteering workers at the manufacturing site. The evaluating MSCA took the proposals for amendment into account, together with the proposals for amendment from another MSCA concerning the same text, and modified the draft decision.

The second PfA was submitted by an MSCA, who noted that the required study is performed in volunteers and proposed to reflect this more clearly in the text. They furthermore noted that when the workers are not willing to cooperate, or when you are unable to find a sufficient number of volunteers, you should document your efforts to undertake the requested study. You did not agree with this PfA, and mentioned the above stated arguments. The evaluating MSCA agreed with the proposed modifications to better reflect the role and consequences of participation of volunteers in this request. The draft decision was modified accordingly to reflect these issues.

The third PfA was provided by an MSCA, who proposed to remove the request for human biomonitoring, or, in the event that the request would remain, to revise the text. This MSCA expressed their concern with regard to requesting a human biomonitoring study in volunteers as a legal requirement, and furthermore questioned what will be done when you cannot comply to the request. Also, this MSCA asked to explore whether the human data you already provided could be used in some way to get a better idea of worker exposure and could illustrate if there actually are concerns (e.g. correlate the blood concentrations with potential exposure). In addition, it was requested to provide more information about the necessity of applying an additional toxicokinetic assessment factor in derivation of the DNEL, and how insight in the human half-life of the registered substance could remove the concern for human health, for workers but especially for the general population. They stated that overall they had some doubts whether the information potentially gained from the human biomonitoring study would be really needed to determine the most appropriate control strategy for workers or if the need to determine the PBT status of the registered substance is the main drive of the request. In the last case, it was doubted whether the data would help in determining the PBT status.

In the event that the request would not be removed, the MSCA suggested to provide more detailed information on the half-lives of PFOA and HFPO-DA in different species, to provide more clearly why the toxicokinetic factor of 66 is used in the risk assessment and what RCRs result from these calculations, why a half-life of 190-h was proposed in an earlier draft of the decision as the threshold for further measurement to determine a (longer) half-life, to clearly state in the draft decision that bioaccumulation is based on a weight of evidence approach, and what key values will be used from the range of half-lives for each substance to assess whether the registered substance is either B or vB. The evaluating MSCA agreed with the proposed revisions, which further clarify the request. You agreed, but stated that you firmly believe the study is not appropriate and should not be conducted.

The MSCA suggested that the human data you provided could be used to correlate to exposure concentration data, to get an idea of the concerns. We have performed these calculations, but the quality of the gained information was low. These calculations are accompanied by large uncertainties, including uncertainty with regard to the exposure conditions and concentrations, and uncertainty involved with sampling only once.

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Further, three outliers, i.e. plasma concentrations that were clearly higher than the main findings, could not be explained and give rise for concern.

Based on the proposed text revisions by the MSCA, more detail was provided concerning the half-lives of HFPO-DA and PFOA in the text as well as in Appendix 5 of the draft decision. Furthermore, in the text a range of RCRs for workers was provided resulting from several exposure scenarios as described in the registration dossier, to illustrate the magnitude of concern. Moreover, the rationale behind the proposed threshold of 190-h (equivalent to a decrease of 20% over 60 hours) in an earlier draft of the decision was explained. In addition, the text was refined as to indicate that the half-life of HFPO-DA would add to the weight of evidence approach for the PBT assessment. It is not the mandate of the evaluating MSCA to determine a threshold indicative of B or vB.

Conclusion

Therefore, based on the substance evaluation and in accordance with Article 46(1) of the REACH Regulation, ECHA concludes that you are required to carry out the following study using the registered substance subject to this decision:

> Human biomonitoring study in volunteering workers at the manufacturing site, as specified above.

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Appendix 2: Procedural history

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to suspected PBT/vPvB and exposure of environment, Ammonium 2,3,3,3-tetrafluoro-2-(heptafluoroporpoxy)propanoate CAS No 62037-80-3 (EC No 700-242-3) was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2017. The updated CoRAP was published on the ECHA website on 21 March 2017. The competent authority of Germany and the Netherlands (hereafter called the evaluating MSCAs) were appointed to carry out the evaluation.

In accordance with Article 45(4) of the REACH Regulation, the evaluating MSCAs carried out the evaluation of the above substance based on the information in your registration(s) and other relevant and available information.

In the course of the evaluation, the evaluating MSCAs identified additional concerns regarding human health hazard relating to carcinogenicity and bioaccumulation.

The evaluating MSCA considered that further information was required to clarify the abovementioned concerns. Therefore, it prepared a draft decision under Article 46(1) of the REACH Regulation to request further information. It subsequently submitted the draft decision to ECHA on 20 March 2018.

The decision making followed the procedure of Articles 50 and 52 of the REACH Regulation as described below.

ECHA notified you of the draft decision and invited you to provide comments.

Registrant(s)' commenting phase

ECHA received comments from you and forwarded them to the evaluating MSCA without delay.

The evaluating MSCA took the comments from you, which were sent within the commenting period, into account and they are reflected in the reasons (Appendix 1). Request 2 was amended.

Proposals for amendment by other MSCAs and ECHA and referral to the Member State Committee

The evaluating MSCA notified the draft decision to the competent authorities of the other Member States and ECHA for proposal(s) for amendment.

Subsequently, the evaluating MSCA received proposal(s) for amendment to the draft decision and modified the draft decision. They are reflected in the reasons (Appendix 1).

ECHA referred the draft decision, together with your comments, to the Member State Committee.

ECHA invited you to comment on the proposed amendment(s).

Your comments on the proposed amendment(s) were taken into account by the Member

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State Committee.

MSC agreement seeking stage

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-62 meeting and ECHA took the decision according to Article 52(2) and 51(6) of the REACH Regulation.

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Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided by you in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on your dossier(s) at a later stage, nor does it prevent a subsequent decision under the current substance evaluation or a new substance evaluation process once the present substance evaluation has been completed.

2. Failure to comply with the request(s) in this decision, or to otherwise fulfil the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

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Appendix 5: Summary of the physico-chemical properties and toxicological profiles of FRD-902 and APFO. Note: these tables are indicative and not comprehensive.

Table 1. Summary of the physico-chemical properties of FRD-902 and APFO

	FRD-902		APFO	
Property	**Value**	**Source**	**Value**	**Source**
Physical state at 20°C and 101.3 kPa	solid powder at 23°C (for the dried substance: 99.4% pure)	ECHA website 2018	Solid	ECHA 2013
	clear colourless liquid at 21°C (for the substance as put on the market; 86% pure; 14.58% water, 7.0 ppm PFOA)	ECHA website 2018; Sinning et al. (2008)		
Vapour pressure	0.0117 ± 0.000115 Pa at 20°C (for the dried substance; 99.4% pure)	ECHA website 2018	0.0081 Pa at 20°C	ECHA 2013; EFSA 2008
	2910 Pa at 20°C (for the substance as put on the market; 86% pure; 14.58% water, 7.0 ppm PFOA)*	ECHA website 2018; [redacted] (2008a)		
Water solubility	1000 g/L at 20°C (for the dried substance; 99.4 % pure)	ECHA website 2018	>500 g/L	ECHA 2013
	>1000 g/L (for the substance as put on the market; 86% pure)	ECHA website 2018		
	>200 g/L	Hoke et al., 2016		
	218 mg/L in well water at 10°C; 207 mg/L in nutrient medium at 10°C***	ECHA website 2018		
	infinitely soluble (>739 ± 13.0 g/L) at 20°C (86% pure; 14.58% water, 7.0 ppm PFOA)	[redacted] (2008a)		
Partition coefficient n-octanol/water (Log K_{ow})	The study cannot be performed due to the surface activity of the substance. The log D (distribution coefficient) of the ionized form estimated at environmentally relevant pHs is 2.58.	ECHA website 2018	0.7	EFSA 2008
Partition coefficient organic carbon/water (log K_{oc})	1.08-1.10 (HPLC method)	[redacted] et al. (2008)	No data	
Melting	208 °C (for the dried	ECHA website	Decomposition	ECHA, 2013

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/freezing point:	substance; 99.4 % pure)	2018	starts above 105 °C	
	-21 °C (for the substance as put on the market; 86% pure)	ECHA website 2018		
	-21 °C (86% pure; 14.58% water, 7 ppm PFOA)	[redacted] (2008)		
Boiling point:	108 °C (for the substance as put on the market; 88% pure; 14.58% water, 7.0 ppm PFOA)	ECHA website 2018; [redacted] (2008)	Decomposes	ECHA, 2013
Dissociation constant	pKa: 3.82 at 20±1°C (for the substance as put on the market; 86% pure; 14.58% water, 7.0 ppm PFOA)	ECHA website 2018; [redacted] (2008b)	2.8	ECHA, 2013
	pKb: 8.10 at 20±1°C **	[redacted] (2008b)		

* The vapour pressure of 2910 Pa is most likely primarily caused by water and ammonia. The lower value of 0.017 Pa should be considered s most appropriate.
** The meaning of this value is unclear (i.e. for which acid-base pair as this value is not complementary to the pKa value).
***Unclear if these values are > values as well.

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Table 2. Summary of half-lives of HFPO-DA and PFOA in four species

	HFPO-DA			PFOA	
Parameter		**Result**	**Reference HFPO-DA**	**Result**	**Reference PFOA**
Half-life mouse (male)	Alpha phase Beta phase	5.8 hours 36.9 hours	Gannon et al., 2016	19 days	Lau et al., 2007
Half-life rat (male)	Alpha phase Beta phase	2.8-3.6 hours 72.2-89.1 hours	Gannon et al., 2016	4-6 days	Lau et al., 2007
Half-life monkey (male)	Alpha phase Beta phase	2.3 hours 64.1 hours	Gannon et al., 2016	20.9 days	Butenhoff et al., 2002
Half-life human (mostly male)		Unknown	-	1378 days	Olsen et al., 2007
Half-life mouse (female)	Alpha phase Beta phase	4.6 hours 24.2 hours	Gannon et al., 2016	17 days	Lau et al., 2007
Half-life rat (female)	Alpha phase Beta phase	0.2-0.4 hours 22.6-67.4 hours	Gannon et al., 2016	2-4 hours	Lau et al., 2007
Half-life monkey (female)	Alpha phase Beta phase	1.9 hours 79.6 hours	Gannon et al., 2016	32.6 days	Butenhoff et al., 2002

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Table 3. Summary of the toxicological profiles of FRD-902 and APFO

		FRD-902		APFO	
Study type	**Parameter**	**Result**	**Reference**	**Result**	**Reference**
Acute oral toxicity rat	LD50	1750 mg/kg bw	[redacted] 2016a	250-500 mg/kg bw	ECHA, 2011
Acute inhalatory toxicity rat	LC50	5.2 mg/l	[redacted] 2016a	0.98-4.6 mg/l	ECHA, 2011
Subchronic toxicity (90-days) rat	Effects LOAEL	Increased A/G ratio Decreased red blood cell parameters Reduction in cholesterol Increased liver weight Increased kidney weight	[redacted] 2016a	Increased absolute and relative liver weight Liver hypertrophy	RIVM, 2016b
	NOAEL/LOAEL	0.1 / 10 mg/kg bw/day	[redacted] 2016a	0.06 / 0.64 mg/kg bw/day	RIVM, 2016b
Chronic toxicity (2 years) rat	Effects LOAEL	Increased A/G ratio	Rae et al., 2015	Decreased body weight gain, histological liver changes	US-EPA, 2016
	NOAEL/LOAEL	0.1 / 1 mg/kg bw/day	Rae et al., 2015	1.3 / 14.2 – 16.1 mg/kg bw/day	US-EPA, 2016
Carcinogenicity rat	Type of tumours	Liver cell adenomas/carcinomas Leydig cell adenomas Pancreatic acinar cell tumours	Rae et al., 2015	Liver cell adenomas Leydig cell adenomas Pancreatic acinar cell tumours	ECHA, 2011
	NOAEL/LOAEL	1 / 50 mg/kg bw/day	Rae et al., 2015	1 / 15 mg/kg bw/day	ECHA, 2011
Developmental toxicity rat	Type of effects	Early delivery Reduced fetal weights	[redacted] 2016a	No developmental effects	ECHA, 2011
	NOAEL/LOAEL	10 / 100 mg/kg bw/day	[redacted] 2016a	150 / -	ECHA, 2011
Generation study mouse	Type of effects	No reproductive or developmental effects	[redacted] 2016a	Resorptions, stillbirth, postnatal mortality, early preputial separation	ECHA, 2011
	NOAEL/LOAEL	5 / - mg/kg bw/day	[redacted] 2016a	- / 1 mg/kg bw/day	ECHA, 2011

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Table 4. Harmonized classification for APFO, and self-classification for FRD-902 as proposed by the Registrant

	FRD-902		APFO	
Endpoint	**Self-classification**	**Reference**	**Harmonized classification**	**Reference**
Acute toxicity oral	*Acute Tox. 4*	[redacted], 2016a	*Acute Tox. 4*	ECHA, 2011
Acute toxicity inhalation	*No classification*	[redacted] 2016a	*Acute Tox. 4*	ECHA, 2011
Skin irritation	*No classification*	[redacted], 2016a	*Inconclusive*	ECHA, 2011
Eye irritation	*Eye Dam. 1*	[redacted], 2016a	*Eye Dam. 1*	ECHA, 2011
Repeated-dose toxicity	*STOT RE 2 (liver, blood)*	[redacted], 2016a	*STOT RE 1 (liver)*	ECHA, 2011
Carcinogenicity	*No classification*	[redacted] 2016a	*Carc. 2*	ECHA, 2011
Reproductive toxicity/developmental toxicity	*No classification*	[redacted], 2016a	*Repr. 1B Lact.*	ECHA, 2011