Chemical Safety Report for the Use of PFOB Containing up to 200 ppm PFOI

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1. INTRODUCTION

AstraZeneca is seeking an exemption from the REACH Restriction on PFOA and PFOA-related substances[1] that would prohibit the use of PFOB (perfluorooctyl bromide) in the manufacture of pharmaceutical products. This is due to the presence in the PFOB of trace levels of PFOI (perfluorooctyl iodide), which is a PFOA-related substance, in a concentration exceeding the threshold set in the REACH Restriction on PFOA and PFOA-related substances. PFOI presence as an impurity in PFOB is inevitable due to the synthetic route for the manufacture of PFOB. AstraZeneca uses PFOB at a manufacturing site in Snäckviken, Södertälje, Sweden for the production of porous particles, which are a functional component in a new generation of AstraZeneca pressurised metered-dose inhaler (pMDI) medicines. These medicines use a novel Co-Suspension™ Technology that contains low-density phospholipid porous particles.

PFOB is used as a processing aid and is critical to delivering the unique aerodynamic properties of the porous particles, which ensure the efficient delivery of the medicine to the lungs.

PFOB is anticipated to be both chemically and biologically stable and is not considered as a PFOA related substance. It was a key component of IMAGENT® (licensed by Alliance Pharmaceuticals, Inc); an injectable suspension for use in patients with suboptimal echocardiograms, which following demonstration of safety and efficacy was approved as a medicinal product by the US Food and Drug Administration (NDA 21-191) in 2002. The PFOB is produced outside the EU and typically contains up to 200 ppm PFOI, which exceeds the threshold of 1 ppm set in the REACH Restriction. It is not possible to source PFOB which meets the REACH Restriction as all synthetic routes proceed via prohibited substances, hence trace amounts inevitably remain in the PFOB.

The porous particles are designed to provide a uniform suspension inside a pMDI, which is able to deliver an optimal distribution of drug crystals in the lungs for alleviation of lung diseases such as COPD[2]. The porous particles also enable consistent delivery of multiple active ingredients from a single pMDI. The technology is utilised in Bevespi Aerosphere which was approved by the FDA in April 2016 for the treatment of COPD. Bevespi Aerosphere is also under marketing review by the authorities in the European Union. There are also other AstraZeneca projects currently in clinical development, such as the fixed-dose triple combination of LAMA/LABA/Inhaled corticosteroid (PT010)[3].

The scope of the exemption request to the REACH Restriction relates to the use of PFOB containing up to 200 ppm of PFOI in the production of porous particles at the AstraZeneca manufacturing facility in Sweden. All subsequent steps in the supply chain are in compliance with the REACH Restriction.

This report discusses the risks with respect to the PFOI impurity in PFOB. It summarises risk management assessments and demonstrates that PFOB is being used responsibly in the manufacture of medicines for the treatment of respiratory diseases.

1.1 European Union and Global Legislation Affecting Use of PFOB

The European Union issued a new regulation under Annex XVII to Regulation (EC) No 1907/2006, the REACH Restriction on PFOA and PFOA-related substances, which will come into force in July

[1] Commission Regulation (EU) 2017/1000 of 13 June 2017, which will come into force in July 2020.
[2] COPD = chronic obstructive pulmonary disease.
[3] Positive late stage clinical results were announced for PT010 in January 2018. AstraZeneca anticipates making regulatory submissions in Japan and China in the second half of 2018, followed by submissions in the US and Europe.

2020. This would prevent the porous particle manufacture described above at the manufacturing facility in Sweden, with significant knock on effects for onward manufacturing activities in France and the UK.

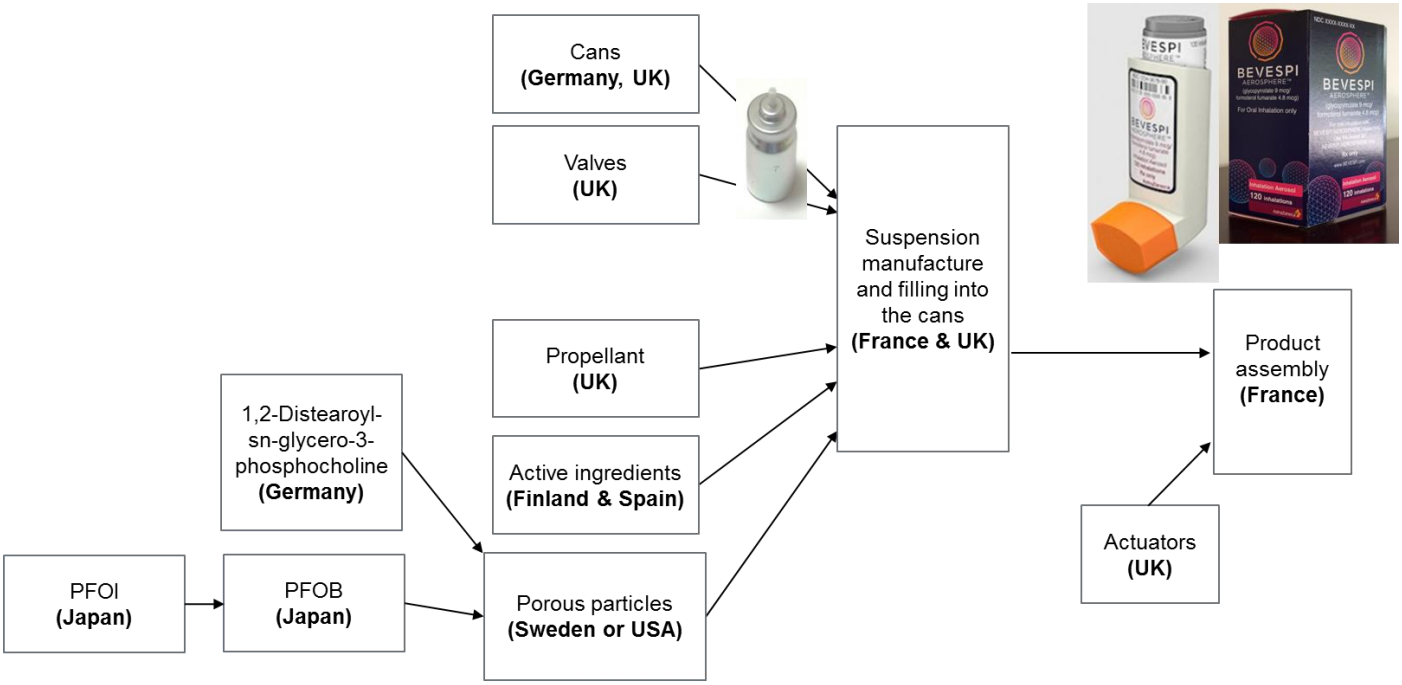
The United Nations Environment Programme (UNEP), under the Stockholm Convention, has also been evaluating pentadecafluorooctanoic acid (CAS No: 335-67-1, PFOA, perfluorooctanoic acid), its salts and PFOA-related compounds. PFOB is exempt from any UNEP proposals, but PFOB is typically synthesised via PFOI which is considered a PFOA related compound. The UNEP Persistent Organic Pollutants Review Committee met in Rome 17th – 20th October 2017 and recommended to adopt the following exemption to ensure medicines are not impacted:

> *"(an exemption) For use of perfluorooctane iodide, production of perfluorooctane bromide for the purpose of producing pharmaceutical products with a review of continued need for exemptions. The specific exemption should expire in any case at the latest in 2036."*

It is anticipated that the exemption described above will be adopted by the European Union eventually, but a time gap is expected between the entry into effect of the REACH PFOA Restriction and the amended global regulation, the length of which cannot be determined at present. Therefore, an exemption is requested to ensure there is not a temporary restriction in place during that time gap, which would force AstraZeneca to move the manufacture outside the European Union, or withdraw the medicines from sale, with potential negative impacts for patients.

1.2 Supply Chain from PFOI through to pMDI Medicines

The Bevespi Aerosphere supply chain has a strong European footprint and is summarised in the flow diagram below:



Note that the PFOB is spray dried away from the porous particle component of the final product, hence there is no significant solvent remaining in the final product, which meets the requirements of the European regulation. The table below shows the levels of PFOI that could be present at each stage in the manufacture of the final product assuming a residual level of PFOI at 200 ppm in PFOB.

Supply Chain Beginning ⟶ **Supply Chain End**

Manufacturing step:	1	2	3	4
Article	PFOI	PFOB	Porous particles	pMDI (final medical product)
PFOI Levels	1,000,000 ppm	200 ppm	0.4 ppm	0.002 ppm
How is the article made?	By-product from C6 telomer process	Bromination of PFOI by-product	Spray dried from a mixture of PFOB and water	Mixture of porous particles, active ingredients and propellant
Location manufactured	Japan	Japan	Sweden or USA (dual sourced)	France or UK (dual sourced)

This exemption request relates to the handling of PFOB during the manufacture of porous particles at the AstraZeneca manufacturing facility in Södertälje, Sweden. The PFOB contains PFOI at levels higher than permitted under Annex XVII to Regulation (EC) No 1907/2006. All subsequent steps in the supply chain are in compliance with the EU regulation.

1.3 Volume Predictions

By 2025, it is anticipated that AstraZeneca will use up to 10 T per annum of PFOB at the Sweden site. The PFOI typically represents up to 200 ppm in the PFOB, hence a maximum of 2 kg PFOI is expected to be handled per annum as a low level impurity in 10T of PFOB. AstraZeneca can manufacture porous particles in the USA but expansion opportunities are limited at the existing facility, so the Sweden site might ultimately manufacture most of the porous particle component of the final pMDI product. AstraZeneca will need to invest in an additional manufacturing suite in 2018 to meet expected supply chain demand and would prefer to make this investment at the Sweden facility.

2. EXPOSURE ASSESSMENT

2.1 General Remarks Regarding the Safety of PFOB

PFOB is not harmful to humans and has been approved by the FDA as a drug product (NDA 020091). PFOB has no known receptor targets and therefore no known biological mode of action. Very little systemic uptake has been observed in mammals following oral administration and bioavailability is considered to be low. In both aquatic and mammalian toxicity studies, PFOB has been shown to be of low toxicity. At environmentally relevant concentrations in the aquatic environment (i.e. up to the limit of solubility) no toxicity to aquatic species is anticipated.

Based on the measured physical-chemical properties and predictive models, PFOB is expected to be biologically and chemically stable and PFOB should be considered as potentially persistent and potentially bioaccumulative.

The handling of PFOB in a controlled environment is therefore of negligible risk to the workforce at the Sweden AstraZeneca facility. The risks from the PFOI impurity are discussed in Section 3. The Sweden AstraZeneca site works closely with local authorities to ensure the site is meeting strict environmental requirements. The site is well established for the manufacture of pharmaceutical products, hence AstraZeneca would like to continue manufacture of the medicinal product at Snäckviken, Sweden, rather than develop the required expertise and manufacturing capability outside the European Union.

2.2 Overview of PFOB use in the Manufacture of Porous Particles

PFOB is used in the preparation of porous particles, which are a functional ingredient in the pMDI products. PFOB typically contains approximately 200 ppm PFOI and the PFOB waste stream therefore contains a proportionately low level (200 ppm) of PFOI.

The porous particles are prepared according to the following stages:

- Preparation of an emulsion (mixture) of $CaCl_2$, water, DSPC and PFOB.
- Homogenisation of the mixture to prepare the feedstock.
- Spray drying of the feedstock to give porous particles.

During the emulsion preparation, DSPC and $CaCl_2$ are dispersed into a vessel containing heated water and PFOB (perfluorooctyl bromide or perflubron) using a high-shear mixer. The coarse emulsion is then further processed with a high-pressure homogenizer before spray-drying using a spraydryer. Gaseous emissions from spray drying are extracted directly from the spray drier and captured through carbon beds in a standalone building. The waste PFOB is removed from the carbon beds for incineration and the carbon bed is re-used.

2.3 Route of Exposure: Workers

Open handling is limited in the manufacturing facility and higher risk activities such as liquid dispensing are managed through use of containment, ventilation/extraction and personal protective equipment, see images below.

Image of extraction unit used during the dispensing/weighing of PFOB.

Image of protective gowns worn by workers during dispensing of PFOB

The most likely route of workers exposure is through inhalation and/or dermal contact. PFOB is not harmful by ingestion, however this is not an anticipated route of exposure in any case. Worker exposure to PFOB is limited by working practices and the risk of exposure to PFOI is further diminished by the high boiling point and very low levels of PFOI present (typically <200 ppm). The risk of PFOI exposure is assessed in Section 3.

2.4 Route of Exposure: Environment

Publicly available data on the environmental fate and effects of PFOB in the aquatic environment is limited. AstraZeneca use of PFOB as a processing chemical is expected to amount to between 1 and 10 tons per annum in the European Union. Therefore, acute aquatic toxicity studies, a ready biodegradation screening assay and determination of the physical-chemical properties of PFOB have been undertaken to support registration under the EU REACH Regulation (No 1907/2006). These studies used PFOB test material from the same source as used in the manufacture of the porous particles, i.e. it contained trace amounts (up to 200 ppm) of PFOI.

Further understanding of the environmental fate and potential for degradation of PFOB has been gained from a quantitative structure–activity relationship (QSAR) model. In this report the environmental assessment and results from the environmental testing, QSAR model and available toxicity data are provided, see Annex: Environmental Fate and Effects Data.

2.4.1 Management of Gaseous Waste

AstraZeneca has installed the best available technology to ensure there is negligible impact on the environment. PFOB is shipped to the Snäckviken site in barrels which are stored in an engine room, then the PFOB is pumped to the manufacturing equipment. The porous particle manufacturing process utilises a mixture of water and PFOB, which are removed from the porous particles during spray drying of the material.

The resulting gaseous PFOB containing PFOI is directed to a dedicated treatment plant where it is passed through dual carbon beds with a total capture rate typically >99.8%. The carbon beds are

equipped with a system that automatically shuts down the manufacturing facility if the emissions exceed the threshold agreed with the local authority. The carbon beds regenerate via in-situ removal of PFOB (containing trace levels of PFOI). As such, no significant releases of PFOI to the environment are expected, particularly as PFOI is present in PFOB at trace levels, typically 200 ppm. 10T of PFOB per annum is expected to be used in Sweden in 2025, this corresponds to <4g per annum PFOI released to the atmosphere as gaseous waste.

To minimise environmental exposure the waste streams containing high concentrations of PFOB and low levels of PFOI are diverted to dedicated tanks before proceeding to off-site incineration at high temperature (at least 1100°C) with 2 seconds residence time for flue gases.

2.4.2 Management of Liquid Waste

Liquid waste from other streams, e.g. dishwashers and laboratories is currently captured for specialised waste treatment by incineration. This liquid waste represents approximately 2% of the total PFOB used, hence the total quantities of PFOI in this waste stream are very low.

This presents a significant amount of incinerated aqueous waste, hence the low concentration waste stream is eventually proposed for treatment at the on-site AZ Waste Water Treatment Facility (WWTF). A Best Available Technique (BAT) is being evaluated with a view to undertake on-site treatment of the low concentration waste stream from the production of porous particles. This would be discussed with the local Sweden authorities.

2.5 Consumer Exposure

The porous particle product is spray dried to remove all PFOB (the control limit is 0.2%). The porous particles represent a small proportion of the final pMDI product, so this controls the levels of PFOI to < 2 ppb in the final pMDI product. This level of PFOI is well within the 1000 ppb limit in the EU regulation and the final products are assessed by medical authorities and have been subjected to extensive trials to demonstrate safety and efficacy of the final product.

Management of potential mutagenic impurities is well established for pharmaceutical products in ICH M7 Guidance[4]. The maximum daily dose for the consumer is approximately 250 mg of the Co-suspension™ product, which at 2 ppb comprises a maximum of 0.0005 micrograms of PFOI in the final product. This provides a 3,000 fold safety factor against the daily threshold of 1.5 micrograms per day in ICH M7 guidance.

2.6 Indirect Exposure of Humans via the Environment

PFOI emissions are calculated to be < 4 g per annum. The low levels of PFOI emitted would be released into a very large air volume and thereby largely diluted because the emission is gradual and gaseous.

Based on total emissions of 16 mg per day, it is extremely unlikely that any single individual, locally and regionally, would be exposed to a hazardous level of PFOI. This is discussed in more detail in Section 3.

[4] ICH Harmonised Tripartite Guideline: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, M7.

3. RISK ASSESSMENT

3.1 DNELs for Workers and the General Population

This section describes how the DNEL (Derived No Effect Level) and risk factors have been considered for PFOI content in PFOB.

PFOI can be broken down to PFOA in the environment and it is likely that PFOI also will be metabolised to PFOA in living organism. To what extent and at what rate is not easy to assess so a very conservative 100% conversion rate is used in this estimate

The critical study for the PFOA is the reprotox study by Lau et al according to the Committee for Risk Assessment (RAC)

https://echa.europa.eu/documents/10162/2f0dfce0-3dcf-4398-8d6b-2e59c86446be

RAC have identified a NOAEL and used estimated serum levels in their DNEL.

Serum levels are hard to use for the described use of PFOB containing trace levels of PFOI, so the administrated oral dose in the critical study described above is used in this assessment.

Critical study: reprotox study in mice (Lau et al)

NOAEL =1mg/kg/d

Recommended assessment factors

Intraspecies, allometric scaling for mice: 7

Interspecies, remaining differences: 2.5

Intraspecies, workers: 5

Interspecies, general population: 10

Total factor for workers: 87.5

Total factor for general population: 175

(RAC uses a total factor of 12.5 (2.5 x 5) since they use serum levels in their assessment and therefore do not have to use the allometric scaling factor.)

DNEL for workers and the general population can then be calculated.

NOAEL = 1 mg/kg/d

Assessment Factor = 87.5

Body weight = 70kg

Assume that bioavailability is the same for oral and inhalation exposure

$DNEL_{workers}$ = 1mg/kg/d / 87.5 x 70 kg =0.8mg/d

$DNEL_{general\ population}$ = 1mg/kg/d / 175 x 70 kg =0.4mg/d

3.2 Risk Factor Ratio for Workers

This can then be compared with a worst case exposure estimate:

AstraZeneca Occupational Exposure Limit (8h Typical Working Average) for PFOB is 1mg/m^3

Default breathing volume over a full workday = 10m^3

PFOI concentration= 200ppm

1mg/m^3 x 10m^3 x 200e-6 = 0.002mg/d

The ratio between worst case exposure and DNEL is then (risk ratio for PFOI):

0.002mg/d / 0.8mg/d =0.0025

This shows a very favourable risk ratio as the worst case PFOI exposure scenario is well below the derived no effect level. The actual margin is larger since the potential for exposure is limited to a few short steps in the manufacturing process and is not 8 hours, 5 days per week. Like PFOA, it is possible that PFOI has a long half-life and there will be some accumulation over time, which is not accounted for in the critical study or in the exposure assessment and this will reduce the margin of safety. Nevertheless, the margin of safety is expected to remain well within acceptable thresholds.

3.3 Risk Factor Ratio for the General Population

Assuming that the Snäckviken site handles 10 T of PFOB per annum, which typically contains a maximum of 200 ppm PFOI, this would represent a total PFOI quantity of 2 kg. The typical carbon capture efficiency of 99.8% would reduce the actual PFOI emissions to < 4 g per annum, typically <16 mg per working day.

The low levels of PFOI emitted would be released into a very large air volume and thereby largely diluted because the emission is gradual and gaseous. As shown in the DNEL assessment, the derived no effect level for humans is 0.4 mg / day. Based on total emissions of 16 mg per day, it is extremely unlikely that any single individual, locally and regionally, would be exposed to a hazardous level of PFOI from this manufacturing process.

3.4 Risk Characterisation for the Environment

Air monitoring is undertaken at the emissions plant and has been demonstrated to be 99.8% efficient at removing PFOB from gaseous emissions. It is calculated that this equates to a maximum PFOI emission of 4g per year based on expected PFOB volumes handled in 2025. All liquid waste is currently incinerated. As such, the manufacturing process does not emit PFOI at levels that pose a significant risk to the environment.

4. CHEMICAL SAFETY REPORT CONCLUSIONS

This Chemical Safety Report demonstrates that the handling of PFOB represents minimal risk to human health and the wider environment. PFOB is not harmful and the residual PFOI impurity in this substance typically represents only 200 ppm.

Current waste management procedures ensure that less than 4 g PFOI per annum would be emitted to the environment with annual use of 10 T PFOB, which is the anticipated volume in 2025.

ANNEX

1. ANNEX - ENVIRONMENTAL FATE AND EFFECTS DATA

1.1 Ecotoxicology

1.1.1 Acute toxicity to *Daphnia magna*

The acute toxicity of the PFOB to *Daphnia magna*, was assessed in study FK88QS, in accordance with the OECD Guidelines for Testing of Chemicals No 202. The water solubility of PFOB in the test media was < 0.02 mg/L, therefore a limit test was conducted with a control, solvent control and single exposure concentration prepared at 0.02 mg/L to determine the toxicity of PFOB at the limit of solubility. The limit of solubility and mean measured concentration of PFOB was 0.011 mg/L. Exposure of *Daphnia magna* to PFOB gave a 48 hour EC50 value of greater than 0.011 mg/L and an observational No Observed Effect Concentration (NOEC) of 0.011 mg/L. This study showed that there were no toxic effects up to the limit of solubility.

1.1.2 Toxicity to the green alga, Pseudokirchneriella subcapitata

The toxicity of the PFOB to the green alga *Pseudokirchneriella subcapitata* was assessed in study NS67LH, in accordance with the OECD Guidelines for Testing of Chemicals No 201. The water solubility of PFOB in the test media was < 0.02 mg/L, therefore a limit test was conducted with a control, solvent control and single exposure concentration prepared at 0.02 mg/L to determine the toxicity of PFOB at the limit of solubility. The limit of solubility and geometric mean measured concentration of PFOB over the test period was determined to be 0.00061 mg/L. Exposure of *P. subcapitata* to PFOB gave a 72 hour EC50 value of greater than 0.00061 mg/L and a statistical NOEC of 0.00061 mg/L. This study showed that there were no toxic effects up to the limit of solubility.

1.2 Environmental Fate

1.2.1 Ready Biodegradation

The potential for PFOB to be readily biodegraded was assessed in study XY05SR, in accordance with the OECD Guidelines for Testing of Chemicals No 301F. In the OECD 301F Manometric Respirometry test, potential for biodegradation was measured indirectly as change in the pressure within the headspace of the test vessel as evolved carbon dioxide was absorbed in a solution of 50% v/v ethanolamine.

The test results show that PFOB attained 66% biodegradation during the 28 day test period. However, the time taken to pass the 60% biodegradation threshold exceeded the 10-day window and PFOB cannot be considered as readily biodegradable.

Although this study appears reliable and to provide evidence of rapid and extensive biodegradation, information available in the literature suggests that whilst biodegradation of some poly- and per-fluorinated compounds is possible, such biodegradation is expected to be incomplete and is unlikely to result in evolution of carbon dioxide, due to the stability of the C-F bond. Whilst dehalogenation and biodegradation of some halogenated organic compounds has been widely and accurately reported, there are no scientific reports in the peer reviewed literature that provide evidence to support the biodegradation of structurally similar compounds to PFOB or compounds with this level of halogenated substitution. Consequently, we conclude that PFOB is not readily or rapidly biodegradable.

1.2.2 QSAR Predictions

To further the understanding of the environmental fate and potential for degradation of PFOB during wastewater treatment a structural-based biodegradation estimate was conducted using the Estimation Programs Interface (EPI) Suite™ program (US EPA, 2012).

Based on its structural properties, the estimated probability of primary or ultimate degradation of PFOB during waste water treatment was low; PFOB is predicted to be recalcitrant. PFOB is not predicted to be readily biodegradable.

The estimated soil adsorption coefficients (K_{OC}) were 5.0×10^5 L/Kg (Kow method) to 1.6×10^6 L/Kg (Molecular Connectivity Index method). K_{OC} provides an indication of the extent to which a chemical is expected to partition between solid and solution phases in soil, or between water and sludge solids in wastewater treatment. The estimated K_{OC} values indicate that during waste water treatment significant removal of PFOB is anticipated via adsorption to sludge solids.

The EPI suite prediction shows good correlation between the estimated vapour pressure 7.62 mm Hg (equivalent to 1016 Pa) and the experimentally measured vapour pressure.

The 'Removal in wastewater treatment' screening model (a model within the EPI Suite™ program) estimates the fate of a chemical as it becomes subject to removal by evaporation, biodegradation and sorption to sludge. This model predicts the full removal of PFOB from waste water during sewage treatment. After entering a waste water treatment system, approximately 59.5% of PFOB in aqueous solution is predicted to be retained on sludge solids and remain within the sewage treatment plant, a further 40.3% is predicted to be removed via losses to air. Overall, following wastewater treatment, exposure of PFOB to the receiving water course is expected to be minimal (<1%). At present, all waste water is incinerated.

1.3 Summary of toxicity data

No biological receptor targets are known for PFOB. Following oral administration, systemic uptake and bioavailability is low. PFOB is regarded to be chemically and biologically stable and inert. The critical effect, based on the available studies, including is general toxicity both long term studies and reproductive toxicity studies, is non-specific general toxicity which was evident in long term studies after repeated dosing. Overall the toxicity of PFOB in test animals was considered to be low.

2. SUMMARY OF ENVIRONMENTAL RISKS

2.1 Potential for Toxicity

PFOB has no known receptor targets and therefore no known biological mode of action. Very little systemic uptake has been observed in animal species following oral dosing and bioavailability is considered to be low. PFOB is likely to be both chemically and biologically stable.

Aquatic toxicity tests on representative algal and invertebrate species show no toxicity up to the limit of solubility. Therefore, toxicity to aquatic organisms is not anticipated at environmentally relevant concentrations.

Based on the lack of biological target and low levels of observed toxicity; both the short- and long-term toxicity of PFOB to species found in the natural environment is anticipated to be low.

2.2 Potential for Bioaccumulation

Although the bioavailability of PFOB via oral exposure has been shown to be very low, the octanol-water partition coefficient is above the bioaccumulation screening criterion established by ECHA (ECHA 2014). Therefore, it is concluded that PFOB may be potentially bioaccumulative.

2.3 Potential for Persistence

Although the results of ready biodegradability test appear to show extensive degradation of PFOB, it is considered unlikely that these results represent true biodegradation. In line with the scientific rationale presented in Section 1.2.1 and the low predicted likelihood of biodegradation within the QSAR model (Section 1.2.2), and in the absence of other evidence indicating non-persistence, it is concluded that PFOB may be potentially persistent in the environment.

3. CONCLUSIONS (ENVIRONMENTAL FATE & EFFECTS DATA)

At full production the proposed used of PFOB is expected to result in a maximum concentration of 0.03 µg/L of PFOB in the receiving environment. This prediction is based on a worst-case exposure scenario and as described in the QSAR calculations (Section 1.2.2), it is anticipated that following the separation of the high PFOB concentration aqueous waste stream for incineration, any residual PFOB entering the WWTF will largely be removed (via adsorption to sludge solids and volatilisation). Therefore, exposure to the aquatic receiving environment is expected to be minimal.

As the worst case predicted environmental exposure is well below the water solubility value, the environmental risk and potential for toxicity to aquatic species in the receiving environment is considered to be low.

The potential for PFOB to be persistent and/or bioaccumulative cannot be ruled out.

To minimize the PFOB exposure to recipient a best available technique will be used to pre-treat the aqueous waste streams resulting in a PFOB concentration below 10 µg/L, prior to further treatment in the WWTF. The aim of pre-treatment is to remove as much PFOB as possible, but 10 µg/L is chosen given the limit of quantification (LOQ) of analysis using GC-MS as an analytical technique. Whilst an LOQ of 1.9 µg/L has been determined for PFOB, the complexity of environmental matrices necessitates a level of 10 µg/L for reliable results allowing for continued understanding and improved mitigation.