ECHA restriction proposal on PFAS - Section IV

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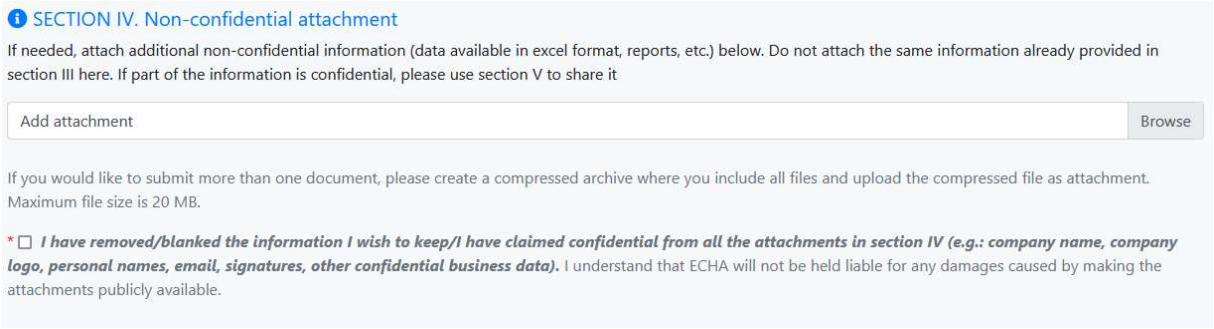
1. Objectives and scope

This document relates to the public consultation from ECHA on a restriction proposal for PFAS. This specific document deals with "Section IV" of the consultation form.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2. Expected benefits of PFOB in the scope of Total Liquid Ventilation

2.1 PFOB and Total Liquid Ventilation

PFOB (Perfluorooctyl bromide) is the Breathable Liquid that enables, when used with Orixha's Liquid Ventilator, to perform Total Liquid Ventilation in comatose patients in order to provide two critical life-support functions for patients in Critical Care:

- support physiological breathing of the patient with a mechanical protection of alveoli from local inflammation,
- support temperature management of the patient with unparalleled ability to cool down the blood compartment and critical organs very precisely and rapidly.

These life-supporting properties open the opportunity for answering a major unmet medical need for resuscitated cardiac arrest patients: ultra-rapid cooling of critical organs to achieve neuro- and cardioprotective therapeutic hypothermia.

2.2 PFOB for hypothermic Total Liquid Ventilation in Cardiac Arrest

The clinical scene that Orixha is addressing with its Vent2Cool solution is Post Cardiac Arrest Syndrome (PCAS).

350,000 Out of Hospital Cardiac Arrests (OHCA) occur each year in the EU and the same number occurs in the US [16]. For these patients, although 30% of them will be resuscitated by Emergency services and brought comatose in Intensive Care Units (ICU), less than 10% will survive eventually. The majority of resuscitated cardiac arrest patients (~110,000 patients / year in EU) will succumb to Post Cardiac Arrest Syndrome (PCAS), for which there is no efficient therapeutic options.

PCAS occurs after prolonged cardiac arrest and causes an inflammatory storm that strikes the vital organs (brain, heart, liver and kidney) in the hours following resumption of spontaneous cardiac circulation. Therefore, PCAS is also referred to as reperfusion injury in the medical literature. PCAS is associated with high mortality (~65%) and morbidity from neurological and cardiac damages.

To prevent the neurological and cardiac sequels of PCAS, the optimal therapeutic approach is to drop the body temperature to 33°C as quickly as possible, therefore achieving neuro- and cardioprotective therapeutic hypothermia. Unfortunately, no current technology can achieve so in less than a few hours, which is inefficient in most patients [17] . The efforts of the first responders and the physicians are wasted. Most survivors are condemned to a "second death" in the hospital post resuscitation.

Hypothermic Total Liquid Ventilation uses the lungs as the most potent heat exchanger and enables a radically new approach for ultra-rapid therapeutic hypothermia, ventilating cold (15 – 33 °C) PFOB in the lungs to reach protective temperature of 33°C within minutes, while current hypothermia medical devices require hours to do so.

It is well known that speed to target hypothermia temperature (33°C) is the dose effect that explains efficacy or lack of efficacy of the hypothermia procedure. Based on its unique cooling speed, Vent2Cool will significantly decrease the mortality and morbidity of PCAS improve survival in good neurologic condition for resuscitated cardiac arrest patients.

2.3 Number of patients

Based on discussions with Key Opinion Leaders and the review of evidence from 10 years of preclinical research on relevant animal models from various species backed by scientific publications [21,22,23], it is expected that Total-Liquid-Ventilation-based Ultra-Rapid Hypothermia induction by Vent2Cool will increase by at least 15% in absolute terms the survival rate from PCAS. With Vent2Cool, PCAS survival will reach more than 50% vs. 35% today with current cooling devices. Once Total Liquid Ventilation based Ultra-Rapid Hypothermia induction by medical devices such as Vent2Cool, is available in all European Cardiac Arrest Centers, and, given that approximately 55% patients will be eligible for Vent2Cool, **it translates into up to 9,000 lives saved per year in the EEA**. By 2030, It is estimated that one third of all eligible patients will benefit from the therapy, with 3,000 lives saved per year.

The 55% eligibility proportion of resuscitated cardiac arrest patients for Total Liquid Ventilation by Vent2Cool is derived from contra-indication and non-inclusion criterias:

- a 5% rate of contra-indications due to the aetiology of the cardiac arrest (namely form traumatic origin inducting the risk of internal bleeding) and,
- a 40% rate of non-inclusion for patients who will be subject to a delay of more than 2 hours from Resumption of Spontaneous Circulation to admission in the ICU therefore reducing drastically the clinical benefit of the Ultra-Rapid Hypothermia induction.

From a medico-economic standpoint, a Quality Adjusted Life Year (QALY) performed by Orixha in 2020 and validated by expert third party (MedC Partners) established an expected gain of 136,000€ per saved patient by Vent2Cool treatment.

2.4 Summary and next steps

In summary, the Vent2Cool solution, that combines a PFOB Breathable Liquid with Orixha's proprietary Liquid Ventilator, is the only ultra-rapid therapeutic hypothermia option and offers a new hope for post cardiac arrest patients combined with significant medico-economic gain for society through its neuro- and cardioprotective effect.

As the leader in the field of Total Liquid Ventilation, Orixha is about to start the clinical validation of its Vent2Cool solution to reach a Technology Readiness Level of 7 with a market approval (CE Mark) expected in 2026. In parallel we are exploring other clinical indications with high unmet medical needs such as specific sub-populations of Acute Respiratory Distress Syndrome patients. The protective properties of PFOB against local lung inflammation would enable better O_2 and CO_2 exchanges in the alveoli. This concerns typically the COVID-19 patients who had to be intubated and for whom the survival rate was around 50% only.

3. Substitution of PFOB In the scope of Total Liquid Ventilation

This paragraph is divided into two different parts. The first part, based on a bibliographic review, describes the different developments that led to discover and select PFOB for Total Liquid Ventilation. The second part summarizes the elements from the first one in a more synthetic way.

3.1 Review of bibliography

Preliminary note :

This paragraph is a review of bibliography, where the terms 'PFC' (for Poly- or PerFluoroCarbons) is generally used. As such, all molecules or families of molecules are hereafter named 'PFC'. They do meet the PFAS definition as per the restriction proposal (see Appendix 1).

3.1.1 Context and discovery of the use of PFC (PFAS) in Liquid Ventilation

Critical Care - the management of critically ill patients - was revolutionized by the development of positive pressure mechanical ventilation since 1950's and extracorporeal oxygenation since 1990's, respectively. Despite these important treatment breakthroughs, there is still a strong unmet medical need for many patients in Critical Care / Intensive Care Units (ICU), whose outcome remains poor leading to a high socio-economic burden. Since the 1960's, it is known that liquid ventilation of the lung for both pediatric and adult patients in ICU could be a new medical breakthrough. Liquids could indeed increase alveolar recruitment at very low pressure and reduce transpulmonary pressure, as well as ventilation / perfusion mismatch. That is the reason why significant research efforts were initiated to identify breathable liquids, that led to the **discovery of perfluorocarbons in the 1960's**.

3.1.2 Partial and Total Liquid Ventilation

PFCs were researched and tested for several medical applications, Iing but not limited to liquid ventilation. Two approaches of liquid ventilation were then described, i.e., partial liquid ventilation (breathable liquid administration during conventional gaseous ventilation) or total liquid ventilation (tidal liquid ventilation using prototypes that infuse/remove the liquid cyclically). The easier technique to implement, partial liquid ventilation (PLV), was first evaluated in patients. Nevertheless, physiological misunderstandings and intrinsic technology limitations led to disappointing results in a pivotal clinical trial of PLV for respiratory distress syndrome with increased risk of side-effects for no clinical benefit [1]. Indeed, the benefits of breathable liquids cannot be revealed with partial liquid ventilation as the connection to a conventional gas ventilator requires high pressure to maintain gas

exchanges through the gas-liquid interface. This inconvenient does not exist during total liquid ventilation (TLV) that exchanges the liquid into the lung and abolishes gas-liquid interfaces, leading to the delivery of "real" liquid ventilation vs. the hybrid approach of PLV. However, TLV technique is much more complIx to implement from a technology standpoint and has not been evaluated in the clinic until now, due the lack of appropriate device to safely ventilate a patient with these liquids. OrixIeveloped a proprietary technology that will allow to perform total liquid ventilation in safe conditions, with multiple benefits in paI in ICU (including hypothermia induction after cardiac arrest, treatment of acute respiratory distress, etc.). In order to translate total liquid ventilation into clinical benefits, Orixha will require the use of PFC as breathable liquids. There is indeed **no alternative to PFCs as breathable liquids**, for several reasons.

3.1.3 Failed attempts in finding alternatives to PFAS in liquid ventilation

Various research projects were initially conducted to identify breathable liquids. For instance, water and water-derived liquids (including saline) were evaluated in the 1960's [2,3]. Solubility for O2 and CO2 were too low to provide oxygen to an alive animal under atmospheric conditions [2,3]. Further studies were conducted with hyperbaric saline solution expecting to increase the amount of dissolved O2 [2,4,5]. Even in those conditions, animals presented immediate respiratory distress before dying from dramatic hypercabia and acidosis. In addition, the use of saline or more general hydrophilic liquids for lung debris lavage inactivates pulmonary surfactant and impairs lung function [6]. This is the reason why two PFCs (Perflubron and Perfluorodecalin) are authorized as a medical device for lung lavage (Liquivent, Origen Biomedic.), beyond liquid ventilation. Among the other liquids with high solubility for O2 and CO2, silicone and vegetal and animal oils were tested as breathable liquids but were all shown to be highly toxic after pulmonary administration [7]. Accordingly, **since 1966, PFCs are known to be the only liquids that could be breathed** [8].

3.1.4 Required performances of a 'breathable liquid' for liquid ventilation

Since that period, researchers and clinicians deciphered the physiology of liquid ventilation and allowed to understand why we could not have alternative to PFC as a respiratory medium [7,9,10]. As a summary, here is a short list of the important characteristics of PFC for liquid ventilation, which explain the lack of substitutes or alternatives:

- high solubility for O2 and CO2 even under atmospheric conditions,
- low surface tension with both air and liquid, leading to high wettability and spreading coefficient (required for a uniform pulmonary distribution and prevention of meniscus in small airways),
- low freezing and high boiling points, respectively (i.e., liquid phase at both room and body temperatures),
- intermediate gas vapor pressure, avoiding excessive evaporation during the liquid ventilation procedure,
- high stability in various use conditions as well as industrial conditions in order to be recycled and reduce the environmental impact,
- ability to be used a reused under antiseptic conditions without modification (i.e., stable after autoclave and/or small-pore filtering),
- minimal absorption through pulmonary administration,
- lack of toxicity.

3.1.5 Chemical properties of PFAS in connection with the required performances

In an attempt to clarify the reasons why PFCs have unique behaviors, Riess [15] summarized the properties of PFCs at the molecule scale, explaining that « … *there are no mysteries, just specific molecules with their rather unique attributes and performances. These attributes derive directly, can be understood and can be predicted from the specific electronic structure and spatial requirement of the constituent atoms, especially the fluorine atom. ».* Among them, « … *the exceptionally high gas-dissolving capacity of PFCs derives from fluorine's extremely low polarizability…*». With no possibility for PFCs to bind gases chemically, the behavior of PFCs regarding O_2 and CO_2 follows Henri's Law and «*… O_2 can be rapidly and extensively extracted from PFCs when needed.* ». In conjunction with their exceptional biological inertness, PFCs have thus a unique potential. Riess concludes that «*… F-compounds offer* ***unique combinations of properties that can make them irreplaceable*** *and constitute the basis for further potential biomedical applications.* ».

In order to further emphasize the importance of these characteristics of PFCs, Alapati and Shaffer [7] recently summarized all these findings : « ... *O2 and CO2 are [...] carried only as dissolved gases with solubilities ranging as much as 16 and three times greater, respectively, in PFC than in saline. Oxygen solubilities range from 35 to 70 ml gas per deciliter at 25°C* [11]*. [...] CO2 solubility [is] approximately four times greater than for O2 (122–225 ml/dl [i.e., PFOB; perfluorooctylbromide [PFOB] = 225 ml/dl]). [...] While many properties of PFC liquids vary, they do provide relatively low surface tension and viscosity, and are more dense than both water and soft tissue. Variations in specific physicochemical properties of the PFC liquids are significant to their use as respiratory media and as vehicles for the administration of biological agents. Fluids of higher vapor pressure may volatilize from the lung more rapidly than liquids having lower vapor pressure. Fluids with greater spreading coefficients (dependent on surface tension) may distribute more easily in the lung than fluids whose spreading coefficients are lower (i.e., FC-75 > PFOB > APF-140). Fluids of higher viscosity or kinematic viscosity may balk at redistribution in the lung, thus remaining in contact with a greater area of the alveolar surface for more time than those stratifying with increased rapidity* [12,13] *resulting in greater flow resistance.* ».

3.1.6 Selection of PFOB among other known PFAS

These findings and rationale led to the selection of PFOB as the best PFC for liquid ventilation. From the 1970's to 1990's, many PFC were evaluated including perflurooctane, perfluorodecalin, FC-75, FC-77, RIMAR 101 and perfluorooctybromide (PFOB). The latter was considered as the most appropriate. Substitutes might be identified among PFC but they would belong to the same chemicals family.

In addition, from an environmental perspective, PFOB is probably one the less-impacting PFC as its gas vapour pressure prevents excessive loss by evaporation as compared to perfluorooctane or perfluorohexane. In a recent review, Kraft and Riess [14] also states that : « *[...]****PFOB [...] stands out among PFCs for medical uses****. It provides a good compromise in terms of excretion rate, O2 and CO2 solubilities, [...] and cost effective high-purity industrial feasibility. The very low equilibrium interfacial tension with water that can be reached in the presence of egg phospholipids, near 1 mN m−1 [...]. Additionally, its radiopaque bromine atom provides contrast for diagnostic radiography, and its positive spreading coefficient (2.7 mN m−1) is advantageous in pulmonary applications.* ».

3.1.7 Conclusion

In conclusion, we consider that **there is no alternative to PFCs for liquid ventilation, among many other evaluated hydro or lipophilic liquids. PFOB seems to be the most appropriate PFC, with a possibility of recycling and treatment after clinical use, in order to prevent environmental impact.**

Once fully deployed, PFOB-based Total Liquid Ventilation is expected to save 9,000 lives per year in the EEA for the sole application in out-of-hospital cardiat arrest (see §2).

3.2 Summary

This paragraph summarizes the information detailed in §3.1 (please refer to §3.1 for full bibliographic justification).

It provides a close look at the use, function, and requirements of PFOB-based Total Liquid Ventilation. It outlines the available alternatives and the technical obstacles that prevent substitution. The analysis of alternatives concludes that there are no appropriate chemical alternatives that could substitute PFOB-based Total Liquid Ventilation.

3.2.1 Function and technical performances

<u>Use</u>

In Total Liquid Ventilation, PFOB 100% is used as the breathable liquid, which is administered by a Liquid Ventilator into the patient's lungs, in a sequence of inspirations and expirations.

<u>Function</u>

PFOB is used as a gas carrier (for oxygen and carbon dioxide) as it allows the gas exchanges with blood circulation through the lung's alveoli.

In the case of post cardiac arrest patients, where Total Liquid Ventilation is used to induce therapeutic hypothermia, the breathable liquid is also a thermal carrier : it allows the withdrawal of thermal energy from the patient.

<u>Safety</u>

Many in vivo studies have been performed to demonstrate the suitability and the lack of toxicity of PFCs, and especially of PFOB, in Total Liquid Ventilation. They also showed a minimal absorption of PFOB through the pulmonary administration.

Orixha is currently conducting a biocompatibility study (cf §4 and section V), as per ISO 10993-x series, to demonstrate the absence of toxicity of its PFOB (in the exact manufacturing and conditioning process). This study will serve as a basis for European Health Authorities to grant Orixha the authorization to perform clinical studies and later by notified bodies to 'CE-mark' the PFOB as a medical device.

Technical performance

PFOB is liquid at ambient and body temperature. PFOB's solubility for oxygen and carbon dioxide is respectively 16 and 3 times greater than water's [11], which allows to use it as a gas carrier into the lung's alveoli. The fluidic properties of PFOB (surface tension, wettability, kinematic viscosity) make it suitable for administration to and from the lungs, down to the alveoli, with safe pressures.

PFOB also does not inactivate the pulmonary surfactant, a substance released by the alveoli and which is key to the lung function.

PFOB has many other properties, such as a high stability (allowing it to be reprocessed and sterilized for reuse) or an intermediate gas vapor pressure (avoiding excessive evaporation during the ventilation procedure).

3.2.2 Identification and assessment of potential alternatives of PFOB

Decades of medical development have failed to identify a suitable alternative to PFCs in Total Liquid Ventilation. Attempts with water, saline water, high solubility liquids such as silicone and vegetal and animal oils were associated with respiratory distress and/or high toxicity.

Since 1966, PFCs are known to be the only liquids that could be breathed [8]. Their unique combinations of properties make them irreplaceable [15]. This is mainly due to the specific electronic structure and spatial arrangement of the constituent atoms, especially the fluorine atom.

All these molecules are PFAS as per the current restriction proposal.

Among all known PFCs that are deemed suitable for liquid ventilation, PFOB has been selected as **the most appropriate one both for its safety/performances as a breathable liquid and its environmental impact. Its evaporation rate is** indeed low enough to avoid any significant losses during the administration. Its high stability is compatible with a reprocessing for reuse, hence offering great opportunities to lower environmental emissions (see Section V).

3.2.3 Identification of human health impacts

Total Liquid Ventilation addresses an unmet need for the 350,000 Post Cardiac Arrest Syndrom patients that suffer from Out-of-Hospital cardiac Arrest every year in the EU. Less than 10% of these patients eventually survive. Total Liquid Ventilation will represent a major breakthrough in the care of the resuscitated patients.

The use of PFOB-based ventilation is expected to save up to 3,000 lives per year in the EEA by 2030 and 9,000 per year once the therapy is fully deployed (see §2).

3.2.4 Conclusion

Out-of-hospital Cardiac Arrest hits more than 350,000 patients per year in the EEA, with current therapies allowing to save less than 10% of them. It is expected that Total Liquid Ventilation would allow to save 3,000 more patients per year by 2030 and 9,000 per year once it is fully deployed in the EEA.

Decades of development have failed to find alternatives to PFCs (PFAS) as breathable liquids. A very unique combination of properties is required to meet both the performances, the safety and the lack of toxicity that are required to perform Total Liquid Ventilation. Scientific state-of-the-art considers that this set of properties can only exist in PFCs.

Among these molecules, PFOB Is deemed the most suitable compromise both in terms of performances/safety/toxicity and for its environmental impact.

This systematic review leads us to believe that there is no appropriate chemical alternative to PFOB for Total Liquid Ventilation and that such alternative will not exist in any foreseeable future.

A restriction on PFOB would thus be synonymous of 9,000 unsaved lives per year in the EEA.

4. PFOB biocompatibility

PFOB has been used in many medical applications, whether at the preclinical or at the clinical stage. The use of PFOB as a medical device is only allowed after tight scrutiny from competent health authorities (Food and Drug Administration in the United States, national health agencies for European clinical investigations, notified bodies for European CE-marking).

Biocompatibility is a main concern of these authorities and manufacturers are to address this concern as per the ISO 10993-x series of International standards. Orixha is currently (spring - summer 2023) performing such studies to demonstrate the innocuity of PFOB administration into the lungs of a patient under Total Liquid Ventilation (see Section V).

These submission files are not necessarily released to the public, which makes the data of preexisting studies only partly available. Still, the available data strongly suggests the absence of toxic risk.

For instance, the Lethal Dose LD50 of PFOB for Intravenous route is as high as 41g/kg of body weight [18].

According to Flaim [19], «… *acute lethality occurred in mice, rats and dogs following single i.v. doses, equivalent to the administration of 1.5 L or more of a 90 % w/v concentrated perflubron emulsion to a normovolemic person weighing 60 kg.*». *The same article mentions that preclinical studies have found no teratogenicity, genotoxicity, cytotoxicity, dermal sensitization, or haemolytic activity associated with perflubron emulsion. ».*

Flores-Aguilar [20] also evaluated the use of PFOB as vitreous substitute and concluded that PFOB Is safe for Intraoperative and long-term use Intravitreally.

Appendix 1 - Molecules

The following tables identifies the molecules mentioned in this document :

Name(s)	Formula	CAS number
Perfluorooctane	C_8F_{18}	307-34-6
Perfluorohexane	C_6F_{14}	355-42-0
Perfluorodecalin APF-140	$C_{10}F_{18}$	306-94-5
Fluorinert FC-75	$C_8F_{16}O$	335-36-4
Fluorinert FC-77	$(C_8F_{18})n.(C_8F_{16}O)m$	52623-00-4
RIMAR 101	$C_8F_{16}O$	
PerfluoroOctylbBromide PFOB Perflubron	C_8BrF_{17}	423-55-2

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