EFCTC Response to "Report and statement of the downsides of HFO refrigerant usage --Impact of fluorochemical refrigerants and their degradation products on the environment and health" by Refolution Industriekälte GmbH Refolution

New report on HFO/TFA adds little to the already detailed understanding of environmental and health effects

The "Report and statement of the downsides of HFO refrigerant usage --Impact of fluorochemical refrigerants and their degradation products on the environment and health" by Refolution Industriekälte GmbH [1] compiles a wide range of publicly available information and does acknowledge that the environmental effects of TFA are considered to be negligible over the next few decades. Some of the statements and conclusions in the report would have benefitted from additional explanation to provide context.

A detailed summary [2] of the effects of TFA has recently been published in 2021 by the Environmental Effects Assessment Panel (EEAP) of the United Nations Environment Programme (UNEP), which provides the latest scientific update on a wide range of issues since their most recent comprehensive assessment (2018). It includes a comprehensive summary for Trifluoroacetic acid (TFA) and points out that most PFAS have different properties from TFA. Some HFCs and HFOs breakdown in the atmosphere to produce TFA. The key points from this summary are in the March 2021 EFCTC newsletter.

HFOs have been subjected to a robust and extensive suite of studies to evaluate their overall safety to humans and the environment. Rigorous risk assessments using this data have been conducted which support their safe use in all intended applications.

This EFCTC response does not comment on every aspect of the report but highlights some statements and conclusions that are potentially misleading without additional explanation.

Contrary to the Refolution Report conclusions, the HFOs have an important role in providing a good balance of safety and performance properties not available with other refrigerants. HFOs have ultra-low GWPs similar to CO_2 and hydrocarbons and will enable net -zero refrigeration and air-conditioning whilst maintaining safety and performance.

EFCTC
Tel. +32.2.436.95.06 anc@cefic.be www.fluorocarbons.org
EU Transparency Register n° 64879142323-90

A sector group of Cefic
European Chemical Industry Council - Cefic aisbl

Additional explanations that provide context for some of the statements and conclusions in the new report from Refolution Industriekälte GmbH

From the Refolution report "The acute toxicity of TFA to mammals is well established (Solomon et al., 2016)"

> The findings of this Solomon et al paper are summarised in the EEAP 2021 paper as "TFA salts are of low acute toxicity to mammals under conditions relevant to environmental exposure". The longer-term toxicity effects of trifluoroacetic acid (as the sodium salt: sodium trifluoroacetate [3]) have been evaluated and characterized in several repeated dose mammalian toxicity studies (see the ECHA REACH registration dossier for TFA).

"Based on the NOEC of 30 ppm (~1.8 mg/kg body wight), the maximum TFA concentration in freshwater in Germany is set to 60 µg/l, but at the same time the german environment agency (UBA) recommends not to exceed 10 µg/l." and in its conclusion *"There is no threat of acute TFA toxicity for humans at any of the current or expected concentrations, but long-term exposure with low concentrations showed elevated ALT-concentrations and indicate that TFA in drinking water can potentially damage the liver and have other impacts, for example on the hormone system."*

> The German drinking water guidance limits for TFA have evolved and increased as more toxicity data has become available. In 2008 the toxicity data was only sufficient for the the German Federal Environment Agency (UBA) to establish a tolerable health value (GOW) of 1 ug/L. After evaluation of further toxicity data the GOW was raised to 3 ug/L. More recent studies allowed the UBA to re-evaluate the calculation of the GOW. In this evaluation, the UBA applies a safety factor of 100 to the NOEC (NOEL No observed effect level) and then adds an additional factor of 10 to allow TFA from drinking water to contribute a maximum of 10% to the tolerable daily intake (TDI). According to the EEAP 2021 paper, rainwater collected in eight locations across Germany in 2018–2019 showed median and a precipitation-weighted mean concentration of TFA of 0.210 µg/L and 0.335 µg/L, respectively, approximately 200 times lower than the allowable maximum in drinking water, and, overall, about 200,000 times lower than the No observed effect level. The EEAP 2021 paper states that "Humans could be exposed to TFA via drinking water and food but there is no evidence to date of adverse effects on health" An item about the drinking water guidance value in Germany is in the March 2021 EFCTC newsletter.

"The toxicity of TFA on aquatic environments is well established. In aquatic environments the selenastrum capricornutum (freshwater green alga) is highly sensitive to TFA exposure with an NOEC of 0.12 mg/l (Boutonnet et al., 1999). A TFA concentration of 100 µg/l is considered to be safe for the aquatic ecosystem (Berends et al., 1999)."

> The EEAP 2021 paper states "Current concentrations of TFA salts and related compounds in soil and surface waters do not present risks of adverse effects in aquatic and terrestrial plants and animals. Historical and current measurements of TFA in soil and surface-water indicate *de minimis* risks when compared to no-[observed]-effect-concentrations (NOECs) in laboratory and field based testing" Additionally, the REACH registration dossier for TFA

EFCTC
Tel. +32.2.436.95.06 anc@cefic.be www.fluorocarbons.org
EU Transparency Register n° 64879142323-90

reports fresh water Predicted No Effect level (PNEC) is 0.56 mg/L based on a significant amount of aquatic toxicity data referenced in the registration dossier (including data referenced in Boutonnet and Berends publications). These levels can be compared to rainwater concentrations reported in the EEAP 2021 paper.

Rainwater mean concentration of TFA (Germany from EEAP 2021 paper)	0.335 µg/L
TFA Reach Registration Dossier PNEC	0.56 mg/L which is 560 µg/L
selenastrum capricornutum (freshwater green alga) NOEC for TFA	0.12 mg/L which is 120 µg/L

"There are many ways to be exposed to fluoride, but the main path is water and nutrition (Guth et al., 2020; WHO, 2004). By releasing fluorinated gases to the atmosphere new ways of exposure are added, possibly effecting peoples that are already at a higher risk of exposure, such as e.g., refrigerant workers."

The Refolution report appears to be confusing fluoride and fluorinated gases. The routes for exposure to fluoride are well established globally (WHO 2006 monograph "Fluoride in Drinking- water" J. Fawell co-ordinator [4]) including from the addition of fluorides to dental products. The WHO 2004 reference states that "Levels of daily exposure to fluoride depend mainly on the geographical area. In the Netherlands, the total daily intake is calculated to be 1.4–6.0 mg of fluoride. Food seems to be the source of 80–85% of fluoride intake; intake from drinking-water is 0.03–0.68 mg/day and from toothpaste 0.2–0.3 mg/day."

The WHO 2006 monograph *[4]* states that waters with high fluoride concentrations occur in large and extensive geographical belts associated with a) sediments of marine origin in mountainous areas, b) volcanic rocks and c) granitic and gneissic rocks. It explains that air is typically responsible for only a small fraction of total fluoride exposure, but it does note that there are some exceptions for example from the indoor combustion of high-fluoride coal for cooking and for drying and curing food.

There is a wide distribution of fluorides in soils, which means that there is significant natural movement of fluoride through the atmosphere on wind-borne dust particles. More information about fluorides is available on the EFCTC website.

"Fleet et al. (2017) pointed out that there is a lack of literature on human health hazards of direct exposure to HFOs."

Reports on exposure of substances to humans may be for example from controlled studies of exposure for specific reasons, such as for the development or use of an anaesthetic, or from investigations of inadvertent exposure, so the lack of available literature for refrigerants is perhaps not surprising. To robustly and ethically characterize the hazards of industrial substances, scientifically validated and well-controlled toxicology studies are

EFCTC
Tel. +32.2.436.95.06 anc@cefic.be www.fluorocarbons.org
EU Transparency Register n° 64879142323-90

conducted according to established test protocols that utilize *in vitro* and *in vivo* model systems. These model systems are designed to allow for a thorough identification and characterization of a substance's hazard(s) to human health.

"Continuous measurements at the Jungfrauenjoch in Switzerland show an increase in concentration and detection of R1234yf over the last decade. The measurements started in 2010 where R1234yf was not detected in the samples. In 2018, R1234yf was measured in 71 % of all the samples. The concentrations increased from 0.002 ppt to 0.050 ppt, respectively."

The detection of HFOs in the atmosphere, with lifetimes of about 10 to 40 days, is no different to the detection of other very short lifetime substances such as propane, isobutane, pentane (non-methane hydrocarbons NMHCs, a sub-set of non-methane volatile organic compounds NMVOCs). These hydrocarbons also have similar atmospheric lifetimes (for example 15 days for propane). The much wider sources of the NMHCs typically lead to substantially higher atmospheric concentrations that can be in the ppb (parts per billion, about 1000 times greater than the HFOs) range, particularly in urban areas. *Explanatory note:* 1 part per trillion (ppt) is **about the same as 1 cm^2 compared to the area of Paris (105.4 sq km). An item about detection of HFOs in the atmosphere appeared in the March 2019 EFCTC newsletter.**

"Additionally, the risk of using R1234yf in mobile air conditioning is higher due to the flammability and chemical reaction of R1234yf in case of a fire or hot surface temperatures. HFO-1234yf is classified by ASHRAE as A2L refrigerant meaning that it is not toxic with a lower flammability than the A2 refrigerants. During an fire or at surface temperatures above 350 °C, R1234yf will form hydrofluoric acid (HF) (BAM, 2009), which is acute toxic (PubChem.)."

In respect of R-1234yf, the EU Joint Research Centre was asked, in 2013, to provide an in-depth analysis [4] of the report elaborated by KBA (Kraftfahrt Bundesamt, German authority responsible for market surveillance and product safety for road vehicles), in order to ascertain whether the results stemming from the tests are well founded and supported by a rigorous and scientific methodology. In particular, the JRC was to clarify if, in the view of the aforementioned report, there is a reason to believe that refrigerant R1234yf may not operate in the vehicles with the appropriate level of safety, in the sense of the General Product Safety Directive (Directive 2001/95/EC) and the Framework Directive 2007/46/EC. The KBA performed a series of tests at three different levels, considering levels 1 and 2 for their assessment of possible risks within the scope of the statutory tasks as product safety authority, and level 3 tests as general risk appraisal. The level 1 and level 2 testing showed no ignition of refrigerant R1234yf and no release of hydrogen fluoride (HF) despite the very high temperatures in the engine compartment. Consequently, the results as such with the vehicles tested under the conditions as described for level 1 and level 2 testing provided no evidence of a serious risk. The refrigerant release tests under level 3 were not taken into account by the KBA as relevant input. The KBA states also that "… (only) the levels 1 and 2 were considered relevant for a risk assessment with respect to the product safety regulations, as only these can be associated with the necessary concrete probability of

EFCTC
Tel. +32.2.436.95.06 anc@cefic.be www.fluorocarbons.org
EU Transparency Register n° 64879142323-90

occurrence." This approach taken by the KBA is supported by the JRC because it reflects JRC's understanding of Article 2(b) of the General Product Safety Directive 2001/95/EC in which is stated *"…'safe product' shall mean any product which, under normal or reasonably foreseeable conditions of use (…) does not present any risk or only the minimum risks compatible with the product's use…"*. Therefore, drawing of conclusions from level 3 tests, further than the ones already drawn from level 1 and level 2 tests regarding the safe operation of the refrigerant R-1234yf in MAC systems, is not appropriate, considering the definition of "safe product" in the General Product Safety Directive 2001/95/EC. This issue was explained in the October 2019 EFCTC newsletter.

"The study showed an increase of the ALT concentration (alanine aminotransferase) depending on the dosage of TFA (Umwelt Bundesamt, 2020). ALT is an indication of damage of the liver such as a liver hypertrophy as it was observed in a 14 day study (ECHA Dossier Für Trifluoressigsäure). In a study to developmental toxicity where TFA was given to pregnant rats (10-20th day of pregnancy) a temporary disfunction (~50 days) of the liver and kidney was observed (GESTIS-Stoffdatenbank)."

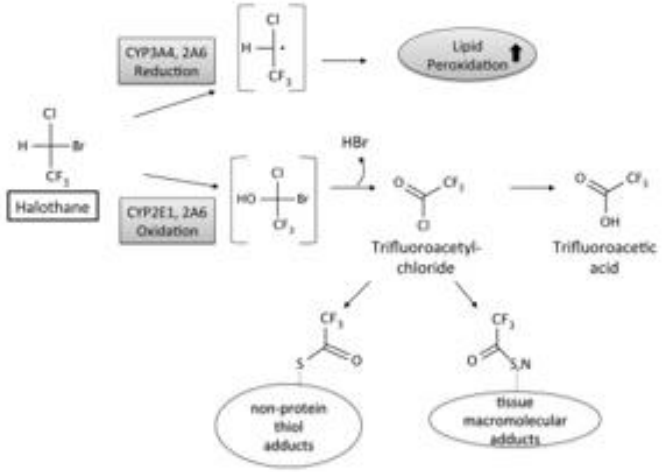
During *in vivo* studies, in-life, clinical pathology, and anatomic pathology parameters are collected and interpreted. To appropriately characterize the overall toxicity to the biological system upon exposure to the test substance, these sets of parameters are evaluated in an integrative manner. Alanine aminotransferase (ALT) is one of many serum liver enzymes that are measured among a suite of clinical pathology markers in rodent toxicology bioassays. Test substance-related changes in clinical pathology parameters are then assessed with respect to changes in the concurrent data sets such as clinical signs and anatomic pathology to determine the underlying pathophysiology. ALT is a clinical pathology parameter that is considered an indicator of an underlying process that has resulted in the change. Such processes can be those that are injurious or adaptive.

The substance exposure levels in such studies, which can include relatively high levels of exposure, are used to determine the No-Observed-Adverse-Effect-Level (NOAEL) and No-Observed-Effect-Level (NOEL). For TFA, the UBA report describes the use of the No-Observed-Effect-Level (NOEL) of 30 ppm as opposed to the higher No-Observed-Adverse-Effect-Level (NOAEL) to derive the Tolerable Daily Intake (TDI) value.

"Halothane oxidation leads to production of trifluoroacetic acid (TFA), which acts on hepatocyte proteins to produce trifluoroacetylated components"

In the chapter on Biochemical Mechanisms of Drug Toxicity. Principles of Clinical Pharmacology (Third Edition 2012) [5] the halothane biotransformation is shown as occurring via trifluoroacetyl chloride and not via TFA. According to the EEAP 2021 paper the half-life for excretion of TFA from the metabolism of anaesthetics in humans was reported to be 16 h.

EFCTC
Tel. +32.2.436.95.06 anc@cefic.be www.fluorocarbons.org
EU Transparency Register n° 64879142323-90



Reproduced from Atkinson J., et al., (2012). Biochemical Mechanisms of Drug Toxicity. Principles of Clinical Pharmacology (Third Edition).

Halothane is metabolized in the liver by cytochrome P-450 (primarily CYP2E1, and to a lesser extent by CYP3A4 and CYP2A6). The biotransformation products include reactive intermediates along both oxidative (trifluoroacetyl chloride) and reductive (free radical) pathways that ultimately generate the metabolites trifluoroacetic acid and fluoride, respectively [6]. The chemically reactive trifluoroacetyl chloride forms non-protein thiol adducts as well as adducts with nucleophilic tissue macromolecules (e.g., proteins, unsaturated lipids) and leads to hepatic injury and potentially fatal hepatitis-like reaction that is characterized by severe hepatocellular necrosis. The free radicals that are formed have been shown to affect lipid peroxidation. The biotransformation of halothane is shown below [5].

"*There is a lack of information in the literature regarding the general effect of fluorochemical refrigerants on the thyroid. But it is known that halogen molecules influence the thyroid function. Therefore, HFO and TFA might also have the possibility to cause hypothyroidism and other consequences such as the brain development of children due to iodine deficiency during pregnancy (Bashash et al., 2017).*"

The Refolution report appears to be confusing fluoride, iodine deficiency and fluorinated gases. The Bashash study is about fluoride intake "The main objective of this study was to assess the potential impact of prenatal exposures to fluoride. It does not refer to TFA or HFOs and has no relevance to fluorinated refrigerants." The Bashash study states that "Community water, salt, milk, and dental products have been fluoridated in varying degrees for more than 60 y to prevent dental caries, while fluoride supplementation has been recommended to

EFCTC
Tel. +32.2.436.95.06 anc@cefic.be www.fluorocarbons.org
EU Transparency Register n° 64879142323-90

prevent bone fractures" In addition the focus of the study is "By virtue of living in Mexico, individuals participating in the study have been exposed to fluoridated salt (at 250 ppm) (Secretaría-de-Salud 1995, 1996) and to varying degrees of naturally occurring fluoride in drinking water." In its conclusion "However, our findings, combined with evidence from existing animal and human studies, reinforce the need for additional research on potential adverse effects of fluoride, particularly in pregnant women and children, and to ensure that the benefits of population-level fluoride supplementation outweigh any potential risks."

Finally, the Refolution report commented that "On land, TFA is believed to have been transported by the mechanical action on the sea, just like sea salt aerosol (EFCTC, 2016). However, this is not plausible since all substances solved in sea water with similar biological, chemical and relevant physiochemical properties for transport are transported similarly. With the assumptions that the sea contains 20 g/L chloride and 20 µg/L TFA as well as 10- 20 mg/l chloride in precipitation, only a TFA concentration of <0.001 µg/l in precipitation can be explained (Nödler et al., 2019)."

However, a more recent 2020 EFCTC paper Transport of naturally occurring trifluoroacetic acid (TFA) by sea salt aerosol offers a possible explanation. However, based on the global annual rainfall, this quantity of TFA if uniformly distributed, would result in < 0.1 ng/L (<0.0001 µg/l *in broad agreement with the report)* in rain, which is insufficient to explain the concentrations measured in the 1990s. If evaporation of TFA occurs within the marine boundary layer during generation of the aerosol, the quantity of TFA introduced into the atmosphere could be very much larger. In the particles of sea salt aerosol, TFA is subject to the same chemical and physical influences as the chloride ion, but with arguably different outcomes. The changes in the aerosol tend to direct the chloride ion towards dry deposition in the particles and wet deposition in rain; chloride ion is not present as a vapour and the 0.4% deposited as HCl remains in the liquid phase. TFA, on the other hand, does have a small but significant vapour pressure over simulated sea salt aerosol and can partition into the gas phase. This possible explanation was explored further in an EFCTC newsletter item Recent paper on ice core records may support natural transport cycle for trifluoroacetic acid.

EFCTC
Tel. +32.2.436.95.06 anc@cefic.be www.fluorocarbons.org
EU Transparency Register n° 64879142323-90

References

[1] Report and statement of the downsides of HFO refrigerant usage -Impact of fluorochemical refrigerants and their degradation products on the environment and health - Refolution Industriekälte GmbH -Published on: 22/02/2021

[2] Neale, R. E., Barnes, P. W., Robson, T. M., Neale, P. J., Williamson, C. E., Zepp, R. G., et al. (2021). Environmental effects of stratospheric ozone depletion, UV radiation, and interactions with climate change: UNEP Environmental Effects Assessment Panel, Update 2020. *Photochemical & Photobiological Sciences*. https://doi.org/10.1007/s43630-020-00001-x. See sections 7.8 to 7.11 for Trifluoroacetic acid (TFA).

[3] As TFA is a strong acid, the effects of the trifluoroacetate group are determined using a neutral salt.

[4] The JRC technical and scientific support to the research on safety aspects of the use of refrigerant R1234yf on MAC systems issued in 2014. The complete report can be accessed with by searching for Ref. Ares(2014)573175 - 04/03/2014

[5] Atkinson J., et al., (2012). Biochemical Mechanisms of Drug Toxicity. *Principles of Clinical Pharmacology (Third Edition).*

[6] Lind, R.C., and Gandolfi, A.J. Covalent binding of oxidative biotransformation reactive intermediates to protein influences halothane-associated hepatotoxicity in guinea pigs. (1991). Adv. Exp Med. Biol. 283:763-6. DOI: 10.1007/978-1-4684-5877-0_102

About EFCTC

The European FluoroCarbons Technical Committee is a Cefic Sector Group that monitors legislation related to HFCs (hydrofluorocarbons), and HFOs (hydrofluoro-olefins) in the EU and at global level.

Fluorocarbons are used as feedstock, as refrigerants, as solvents and as blowing agents for insulation plastic foams.

Contact: **EFCTC Chairman:** Dr. Nick Campbell, nick.campbell@arkema.com
EFCTC Secretariat: Angelica Candido, anc@cefic.be

EFCTC
Tel. +32.2.436.95.06 anc@cefic.be www.fluorocarbons.org
EU Transparency Register n° 64879142323-90