Introduction

Given the high level of misinformation regarding the origins of TFA, it would be important to clarify in this introduction that TFA is NOT of natural origin. Several scientific publications can be cited as references to refute the claim that TFA could have a natural origin, an argument that is too often used by the industry to downplay the impact of their own emissions:
- Joudan S, De Silva AO, Young CJ. Insufficient evidence for the existence of natural trifluoroacetic acid. Environ Sci Process Impacts. 2021 Nov 17;23(11):1641-1649. doi: 10.1039/d1em00306b
- Finnian Freeling, Maria K. Björnsdotter, Assessing the environmental occurrence of the anthropogenic contaminant trifluoroacetic acid (TFA), Current Opinion in Green and Sustainable Chemistry, Volume 41, 2023, 100807, ISSN 2452-2236, https://doi.org/10.1016/j.cogsc.2023.100807.

In the sentence "Trifluoroacetic acid (TFA) is primarily of anthropogenic origin", the word "primarily" should be deleted

Assessment

- **Repeated oral toxicity**

Generations Futures disagrees with EFSA's conclusions on the 52-weeks study (reference #109) and with the NOAEL set for this study at 37.8 mg/kg bw/d

EFSA adopted the same conclusion as that made by Solvay, namely that no adverse effects were found in this study. However, this conclusion contrasts significantly with the conclusion of the German agency UBA, which conducted a detailed analysis of this study in 2020 (report called "Ableitung eines gesundheitlichen Leitwertes für Trifluoressigsäure (TFA)"):
UBA received the unabridged original report, including all essential parameters of the individual animals. After an in-depth analysis of the data, UBA found that the critical endpoint in this study is ALT elevation. According to UBA, the causal link between TFA administration and the increase in ALT is clearly established by the decrease in ALT levels after stopping TFA administration. An analysis of the data using ANOVA (analysis of variance) shows significant differences ($p = 0.005$ and 0.009) between the ALT concentration in the control group (0 ppm TFA) and the groups with 120 ppm and 600 ppm TFA on day 370. UBA therefore identified a NOAEL due to a dose-dependent increase in ALT levels at 120 ppm (equivalent to 1.8 mg/kg b.w/d).

Therefore, The NOAEL for the 52-weeks study should be 1.8 mg/kg b.w/d instead of 37.8 mg/kg bw/d.
The NOAEL of 1.8 mg/kg b.w/d should be used for the calculation of the ADI.

Moreover, we disagree with the assertion that "changes in haematological parameters observed across studies were mild and were not considered to reach the relevant level of adversity". For instance, an increase in ALT is a clear marker of liver damage or disease.

- **Multigeneration reproductive toxicity**

We disagree with the EFSA conclusion on the EOGR study: Indeed, EFSA concludes TFA-Na did not impair reproductive performance but also recognises that changes in sperm parameters were observed in both generations at the highest dose. This is totally inconsistent and EFSA should have concluded that reproductive capacity was altered in this study. This effect on sperm parameters should be considered in relation to the disruption of the viability and function of both isolated Leydig and Sertoli cells, as well as the Sertoli cell-only cultures (SCOC), and Sertoli-germ cell co-cultures (SGCC) found in the mechanistic study #169

More over, the changes in clinical chemistry parameters (i.e. decreased levels of glucose, non esterified fatty acids, triglycerides, and cholesterol) must be considered as "adverse"

- **Immunotoxicty**

The decrease in absolute cell counts in the spleen, observed in both sexes and at all dose levels must be considered as an adverse effect in the EOGRTS

- **Uncertainties**

- With respect to the lack of DNT study:
As acknowledged by EFSA, "a concern for developmental neurotoxicity (DNT) related to TFA cannot be excluded given the decrease in thyroid hormone levels observed in the EOGRTS". We totally disagree with the way EFSA has addressed this concern. According to EFSA, the NOAEL of 8.65 mg/kg bw per day (based on decreased T4 levels at 44.3 mg/kg bw per day and higher) is considered conservative and protective of potential DNT effects because the NOAEL was selected "at the dose just below the one at which decreases in thyroid hormones levels were observed". This justification is completely unacceptable and insufficient. Actually, EFSA just explained how a NOAEL (and it is important to remind the signification of the acronym NOAEL: No Observed Adverse Effect Level) is selected!
Without performing a DNT study, it is impossible to say that this NOAEL is protective of DNT effects

- With respect to clinical chemistry findings:
Line 428-430: the increases in liver enzymes, (alanine aminotransferase (ALT)) is statistically significative and should be considered as adverse

- With respect to immunophenotyping findings:
The reduction in the total number of splenic immune cells should not be downplayed, as EFSA did, and must be regarded as an adverse effect.

- **Setting of consumer health-based guidance values**

Generations Futures disagrees with EFSA's approach:
- First, the NOAEL used for calculating the ADI should be the NOAEL of 1.8 mg/kg b.w./day found in the 52-week study in rats.
- Given the significant uncertainties regarding TFA toxicity—specifically, the lack of cancer studies, the absence of DNT studies despite the decrease in thyroid hormone levels observed in the EOGRTS, and the lack of immunotoxicity studies—a higher safety factor should be applied. In the absence of any chronic studies, an uncertainty factor of 10 should be used, in addition to the standard assessment factor of 100, resulting in a total uncertainty factor of 1000. The resulting ADI should therefore be 0.0018 mg/kg b.w/d

Conclusion

The ADI should be equal to 0.0018 mg/kg b.w/d

Recommandation

Given that TFA is now ubiquitous in the environment and that its concentrations are rising across all environmental media because of its persistance, along with the fact that everyone is exposed to TFA through drinking water and food, we cannot afford to have any uncertainty regarding its toxicity.

That's why the recommandations of EFSA are completely unacceptable and not sufficient at all! We absolutely need to have a chronic toxicity and cancerogenicity study. EFSA acknowledges itself that the 52-weeks study does not meet the criteria for a full carcinogenicity assessment. Therefore, a cancerogenicity study conducted according to OECD 451 and/or 453 must be performed.

Also, as a concern for developmental neurotoxicity (DNT) related to TFA cannot be excluded given the decrease in thyroid hormone levels observed in the EOGRTS, it is necessary to perform a DNT study according to OECD 426.

New reproductive study must be conducted to address the uncertainties regarding the effects of TFA on sperm parameters

Finally, a complete assessment of the immunotoxicity potential of TFA must be performed.