Honeywell

Annex III. – Comments on TFA toxicologic and risk assessments in the Proposal for PFAS REACH Restriction

1. Hazard and Risk associated with Trifluoroacetic acid (TFA) exposure

Trifluoroacetic acid (TFA) (CAS: 76-05-1), a strong acid with pH of 0.45, ionizes completely in the water and exists mostly in sodium or potassium salt. Pure (neat) TFA, because of its acidic properties, can cause skin corrosion, eye damage and respiratory irritation. Currently, TFA has been classified for skin corrosivity and eye damage (due to acidic nature), and acute inhalation toxicity as per CLP and GHS. Note that such hazards are irrelevant at reported environmental concentrations in water. In diluted form, many strong acids are safe (e.g. dilute acetic acid is vinegar, diluted phosphoric acid is a common beverage additive etc.). These other acids are diluted to levels that are still many orders of magnitude higher than the environmental concentrations of TFA.

Several scientific publications such as Solomon *et al.* 2016, Dekant and Dekant, 2023, and **UNEP 2022 (EEAP) report** summarizes the toxicity profile of TFA[1] [2] [3]. UNEP, 2022 report concludes that TFA does not interact with biological molecules and concentrations are so low that it is very unlikely to have adverse toxicological consequences for humans and ecosystems out to 2100. Dekant and Dekant, (2023) through a risk assessment have demonstrated the actual health risk to the general public from TFA exposure is minimal as the Margin of Exposure (MoE) to humans is 4,000 to 476,000 times, indicating that the levels of TFA in the environment are several magnitudes below what would be considered toxic.[2]

We take the public commenting opportunity to point out several key points of disagreement on TFA toxicity envisaged in the **Proposal for PFAS REACH Restriction** by providing scientific rationale and justifications. We trust that the RAC considers the factual scientific information and draws objective conclusions on TFA hazard and most importantly on the risk associated with TFA exposure.

2. Contradictory statements on TFA toxicity to humans in Annex B of restriction proposal

The **PFAS ANNEX XV restriction report** (hereinafter – **Report**, see section 1.1, Page 30) states that, "*concerns for human health by TFA itself are LIMITED to effects at high doses in experimental animals: liver effects (increased liver weight, hepatocellular hypertrophy, increased ALT), increased kidney weight, decreased white blood cells, reduced weight of reproductive organs, litter loss, reduced body weight of offspring, and malformations (see Annex B.5.2.)*"[4]

We agree with this statement. As mentioned earlier TFA being a strong acid is expected to have certain health hazard upon acute exposure to neat substances. Undiluted trifluoroacetic acid is highly corrosive on contact with skin, and inhalation of pure trifluoroacetic acid irritates the upper airways. As undiluted trifluoroacetic acid is only handled in industrial applications and laboratories with adequate safety measures, the hazard information has little relevance to human exposure from the environment, since environmental exposures are limited to diluted TFA or its salts.[2]

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[1] Solomon K, Velders G, Wilson SR, Madronich S, Longstreth J, Aucamp PJ, Bornman JF (2016), *Sources, fates, toxicity, and risks of trifluoroacetic acid and its salts: relevance to substances regulated under the Montreal and Kyoto Protocols.* J Toxicol Environ Health B Crit Rev, 19(7):289-304.

[2] DeKant W and DeKant R, *Mammalian toxicity of trifluoroacetate and assessment of human health risks due to environmental exposures,* Archives of Toxicology (2023) 97:1069–1077.

[3] *Environmental Effects of Stratospheric Ozone Depletion, UV Radiation, and Interactions with Climate Change : UNEP 2022 Assessment Report of the Environmental Effects Assessment Panel*

[4] Page 30 from section 1.1. Hazard, exposure / emissions, and risk / from section 1.1.4. Hazard assessment / from section 1.1.4.9. Effects on human health.

For risk assessment purposes the effect on liver from a GLP-compliant OECD 408, repeated dose oral toxicity study in rats has been selected for point of departure by various agencies. Based on the adverse effect in the liver, no observed adverse effect levels (NOAELs) of 8.4 and 10.1 mg TFA/kg body weight per day in male and female rats, respectively, was determined. In a separate GLP compliant, 1 year drinking water study, as per OECD 452, with NaTFA was conducted in rats. In this study, no treatment-related adverse effects were observed and NOAELs of 37.8 and 64.0 mg TFA/kg body weight per day for male and female rats, respectively, were determined based on changes in activity of the enzymes alanine-amino-transferase (ALT) in the blood without concurrent microscopical changes in the liver. UNEP, 2022 report has also reviewed this report and concludes that "increases in the activity of enzymes in or originating from the liver are considered as compensatory unless accompanied by physiological responses such as loss of weight. This reported effect does not change the conclusion that TFA is of low toxicity in mammals [3]". Based on the scientific evidence, the liver can be considered as the target organ of toxicity for TFA in rodent models. The target organ effects observed on the liver in the animal studies appear to be mediated by peroxisome proliferation via interaction of TFA with the peroxisome proliferated-activated receptor alpha (PPARα)[5]. In the context of the human relevance framework, PPARα interaction with subsequent proliferative hepatic effects is a mode of action not considered relevant to humans [2 6].

Further in Annex B (page #5) of the Report, it is stated that "*Trifluoromethyl fragments are also linked via degradation to trifluoroacetic acid (**TFA**) which has been demonstrated to be a persistent substance with harmful properties in a **COMPARABLE** way as other PFASs with longer fluorinated alkyl chains."* This is a misleading and erroneous statement. It is well established that several chemicals in PFASs family are known to have hazardous properties like carcinogenicity, reproductive toxicity, endocrine disruption etc. With respect to TFA, although persistent, its toxicity is not comparable to conventional longer chain PFAS molecules. TFA has low Octanol/Water coefficient (P_{ow} of 0.79) and does not trigger any bioaccumulation and biomagnification in food chain and has not been classified as CMR after thorough scientific review of experimental studies. Thus, TFA cannot not be categorized as having harmful properties similar to long chain PFAS molecules: *"Trifluoroacetic acid has biological properties that differ significantly from the longer chain polyfluoroalkyl substances (PFAS) and inclusion of TFA in this larger group of chemicals for regulation would be inconsistent with the risk assessment of TFA."* [3]

It is concerning that there are contradictory statements on TFA toxicity in the Report as such vs Annex B thereof. For example, EU-PFAS ANNEX XV restriction report (page 30) states that "*concerns for human health by TFA itself are **LIMITED** to effects at high doses in experimental animals" which contradicts with statement from Annex B (page# 5) "with harmful properties in a **COMPARABLE** way as other PFASs with longer fluorinated alkyl chains".* Several publications such as Solomon *et al.* 2016 and, Dekant and Dekant, 2023 summarize the toxicity profile of TFA. Through a proper risk assessment they have demonstrated the risk to the general public from TFA exposure is minimal as shown via the Margin of Exposure (MoE) to most humans is 4,000 to 476,000 times, indicating that the levels of TFA in the environment are several magnitudes below what would be considered toxic[1, 2 3]. Similarly, Solomon *et al.* 2016 have reviewed the environmental and mammalian toxicity profile of TFA and concluded that *"the current and estimated concentrations of TFA in the atmosphere do not present a risk to humans and the environment."* All current scientific literature available clearly conclude that based on recent levels of TFA in water and diet, there is a significant margin of safety for human exposures to TFA and it presents minimal human health risk. The plethora of information agrees with Annex B statement that "*concerns for human health by TFA itself are*

[5] Bayer C (2014): *Summary of toxicological and metabolism studies for flurtamone*. https://www.bayer.com/sites/default/files/M-482307-01-5.PDF

[6] Felter SP, Foreman JE, Boobis A, Corton JC, Doi AM, Flowers L, Goodman J, Haber LT, Jacobs A, Klaunig JE, Lynch AM, Moggs J, Pandiri A (2018), *Human relevance of rodent liver tumors: key insights from a Toxicology Forum workshop on nongenotoxic modes of action*, Regul Toxicol Pharmacol 92:1–7.

LIMITED *to effects at high doses in experimental animals"* but contradicts the statement that *"with harmful properties in a* ***COMPARABLE*** *way as other PFASs with longer fluorinated alkyl chains".*

3. Neither Hydrofluoroolefins (HFOs) nor TFA have thyroid toxicity

The document (page #158, Annex B.5 of the Report) makes a statement on '*Thyroid effects in experimental animals – Non-polymeric PFASs' by saying that for TFA and HFCs or HFOs there are almost no indications for thyroid effects, which may partially be explained by the limited available data*". This overarching statement disregards the empirical scientific evidence conforming no thyroid toxicity potential. Thyroid effects, either directly or indirectly, have been evaluated for HFOs in repeat-dose toxicity and reproductive developmental toxicity studies by measuring the weight of thyroid organ, level of thyroid hormones and/or by thyroid histopathology. Overall, no thyroid toxicity has been observed for HFOs such as 1233zd(E), 1234ze(E), 1234yf, which are currently placed on the EU Market[7,8,9]. With regard to TFA, a GLP compliant extended one generation toxicity study reported no changes in TSH of F0 males at 600 or 3000 ppm, and in F1 males and females. In the same study, mean serum T_4 concentrations were low in F0 males at 3000 ppm and in females at 3000/1500 ppm, and at 1500 ppm concentrations for F1 male and female offspring on Day 22 of age, compared to Controls. However, considering that there were no effects on TSH hormone, reproductive performance, parturition, offspring, survival, clinical condition or sexual maturation, and changes in the reproductive organs (all parameters/processes depending on normal thyroid function), the low T_4 levels observed **do not represent an adverse effect of treatment**. In addition, no treatment related changes are reported in thyroid histopathology in the same extended one generation study and in a separate 90-day repeat dose toxicity study[10]. The weight of evidence strongly suggests that TFA do not have effect on thyroid systems and should not be compared with molecules having longer fluorinated alkyl chains.

4. TFA has no immunotoxic characteristics

Annex B (page# 159) of the Report also makes erroneous statement on immunotoxicity of TFA. It is stated that "*In support of the epidemiological evidence, immunotoxic effects have been observed in animal studies for a variety of different PFASs. The following effects have been reported for PFASs across many PFAS subgroups, such as PFAAs, PFEASs, and some fluorinated gases. Reduction of lymphoid organ weights was observed for, e.g., PFHxA (Loveless et al., 2009), PFOA, PFNA, PFDA (NTP, 2019a), F-DIOX (RTC, 2011), CAS No. 524709-77-1 (Non-Clinical Saftey, 2017). Changes in lymphocyte counts or proliferation were observed for, e.g.: -TFA (BayerCropScience, 2014)*"

TFA has been cited to have immuno-toxic effects because of decrease in total lymphocyte count in females at the highest dose of 2400 ppm in a 14-day oral dietary study with TFA. However - in the same study, there was no change in total absolute neutrophil count, and it was concluded that that change in absolute count in lymphocyte is considered to be toxicologically non-relevant. It was concluded that observed effect was a random effect and of not a biological significance as none of other sub-chronic and chronic studies had reported similar effect on lymphocyte count.[11] Separately, an extended one generation reproductive toxicity study performed with TFA concluded that there is no developmental immunotoxicity hazard associated with TFA.[8] Hence, the casual conclusion in the PFAS restriction proposal that TFA is an

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7 ECHA (2023), 1234ze(E): https://echa.europa.eu/registration-dossier/-/registered-dossier/31292

8 ECHA (2023), 1234yf: https://echa.europa.eu/registration-dossier/-/registered-dossier/16012

9 ECHA (2023), 1233zd(E): https://echa.europa.eu/registration-dossier/-/registered-dossier/10762

10 ECHA (2023), TFA: https://echa.europa.eu/de/registration-dossier/-/registered-dossier/5203/7/1, European Chemical Agency: Registration dossier for trifluoroacetic acid EC number: 200-929-3; CAS number: 76-05-1 (first published 03-Mar-2011, last modified 10-Oct-2022, accessed April-2023)

11 *BayerCropScience (2014): Summary of the toxicological and metabolism studies for flutamone*. BayerCropScience, https://www.cropscience.bayer.com/sites/cropscience/files/inline-files/M-482296-01-5.PDF

immuno-toxicant is scientifically not justified. We would request the RAC to consider all scientific information before making any conclusion on TFA immunotoxicity.

5. TFA is not teratogenic

Annex B (page# 161) of the Report states that "*Adverse effects on reproduction in experimental animal models, such as total litter loss and perinatal/postnatal mortality, have been observed for a variety of non-polymeric PFASs with different chemical structures. (Total) Litter loss was observed in experimental animal models after exposure to TFA (Covance Laboratories, 2020a)*" Above statement on TFA cites a non-GLP dose range finding study with rabbits[12]. In this study, pregnant rabbits were administered 250, 500, and 1000/750 mg/kg/day of TFA via oral gavage during GD6 to GD 28. However, a GLP OECD compliant main study was conducted evaluating all standard parameters. This main PNDT study (at 180, 350, and 750 mg/kg/day) which was performed on the basis on the preliminary non-GLP dose range finding study did not establish any relevant effect on litter size. Additional details can be found in TFA ECHA dossier[8].

6. Relevance of developmental toxicity of TFA in rabbits to human health risk assessment

Annex B (page# 162) of the Report states that "*Some PFASs caused developmental malformations In offspring of experimental animal models: TFA (Covance Laboratories, 2020b)*".

There is GLP compliant rodent and non-rodent PNDT study available with TFA. In the PNDT study with rabbits, fetal abnormalities beyond the historical control incidence, primarily affecting the eyes were observed at the two highest dose levels. In this study, 11 out of 11 of fetuses at 750 mg/kg/day and 5 out of 8 of fetuses at 375 mg/kg/day showed retinal folding effect. Only one incident of retinal folding was observed at 180 mg/kg/day which was within historical control dataset. In addition, such effects are observed only in the rabbits and not in rats indicating that there is species sensitivity to this end point and needs further investigations.

Although, a NOAEL for embryo-fetal developmental toxicity was not established in the PNDT study with rabbit because of improper dose selection; the observed incident rates strongly suggest a threshold effect. A clear NOAEL can be established by selecting doses lower than current dose regimen in the rabbit PNDT study. In absence of established NOAEL (in this study), as a common toxicological practice, a point of departure for human health risk assessment can be established with use of uncertainty factors and/or benchmark dose modeling analysis. Moreover, a risk assessment with a very low NOAEL of 10mg/kg/day shows that margin of safety of 4,000 to 476,000 times at current reported TFA environmental concentrations. New developmental toxicity finding would not change the conclusion of the risk assessment by Dekant and Dekant [2].

CONCLUSION:

TFA is a strong acid and therefore (like any other strong acids) has certain hazards at high concentrations in industrial setting. Such hazards can be mitigated with proper use of PPE while handling neat TFA and are of no relevance for environmental concentrations.

As discussed in detail previously, the systemic or developmental toxicity observed in experimental animals at high concentrations suggest a threshold mechanism. The toxicity observed in rat liver is considered to be a key end point for human health risk assessment [2]. Although this end point is human irrelevant (due to rodent specific mode of action), Dekant and Dekant (2023) has established a safety margin, for human

[12] *Covance Laboratories (2020b): Sodium Trifluoroacetate: Study for Effects on Embryo-Fetal Development in the New Zealand White Rabbit by Oral Gavage Administration*. 8437242. Covance Laboratories Limited, Eye Suffolk, IP23 7PX UK

health risk, that is much higher than the level of concern (4,000 to 476,000 times). UNEP, 2022 report also concluded that current and projected risk to human health and ecosystem from very low concentration of TFA is de minimis even out to year 2100.

Nevertheless, the Report has presented the toxicity of TFA in an unscientific manner and deemed it comparable with that of PFAS molecules with longer fluorinated alkyl chains. In principle, each chemical (TFA) should be evaluated based on its own toxicity characteristics and not compared with a class (PFAS), especially when the data suggests otherwise. We request RAC to consider all information available to draw conclusions for TFA toxicity on its own, and not assign TFA to the same group as longer chain PFAS molecule, as TFA is not comparable to these PFAS chemicals from a toxicological risk analysis.