PAN Europe's comments on CLH report on Trifluoroacetic Acid

Overall

PAN Europe welcomes the opportunity to provide comments on the ECHA's CLH report on the new hazard classes of TFA.

Our organisation is closely following the developments related to TFA, as it is a common degradation product of 30 PFAS pesticide active substances used in numerous pesticide products across Europe. The use of PFAS pesticides has increased over the past 10 years, as we can see by rising residue levels in fruit and vegetables, as well as in sales data, where available. Most PFAS pesticides contain at least one -CF3 group and are a significant source of TFA contamination into the environment and water resources. Our preliminary work has shown that TFA is detected in water resources across all Europe, including drinking water, both tap or mineral bottled water, as well as groundwater.

Given that human and environmental exposure to TFA is already widespread and rapidly increasing, it is of utmost importance to conduct an objective, independent, and thorough investigation of the toxicity of this common pesticide metabolite. As this issue concerns multiple PFAS substances, the assessment process must be protected from industry attempts to downplay the toxicity of the substance.

Scientific evidence clearly indicates the potential of this very persistent and very mobile metabolite to impair fertility and foetal development. A correct classification of its hazard properties will support political measures to remove the relevant pesticide products from the market- as well as other TFA emitters - and ensure better protection of public health, now and for future generations.

Comments on hazard classes

10.10 Reproductive toxicity

10.10.1 Adverse effects on sexual function and fertility

We welcome the review of the original EOGRTS (TG 443) by the dossier submitter highlighting the identified adverse effects, since the registrant had not reported any adverse effects in its report of this study. The reduction of sperm quality in rats, however, should be considered as a significant adverse effect, even though it doesn't lead to a significant effect on reproductive success of the parental generation in rats. Given that the rat has larger sperm reserves than humans, as correctly stated in the report, it is very probable that fertility in humans is more sensitive, as a response to reduced sperm quality, than rodents.

10.10.4 Adverse effects on development

We support the classification of TFA as **"presumed human reproductive toxicant" Category 1B**, which is fully supported by the available evidence from studies in rabbits and rats.

Two guideline developmental toxicity (DevTox) studies (OECD TG 414) from 2021 and 2024 in rabbits clearly demonstrate TFA's potential to cause developmental effects in offspring. In both studies, exposure to TFA resulted in foetuses exhibiting skeletal abnormalities (including cervical, thoracic, lumbar, and caudal vertebral and rib malformations) as well as eye malformations, such as multiple-folded retinas and absent aqueous or vitreous humour, among other effects.

The **evidence is strong** as these adverse effects on foetuses were seen in the 2021 DevTox study at all exposure levels (180, 375, 750 mg/kg bw/day) as well as in the follow up 2024 study (30, 60, 250, 750 mg/kg bw/d) at exposures from 60 mg/kg onwards, establishing a NOAEL of 30 mg/kg. In addition, there was no maternal toxicity was observed, and the adverse effects are irreversible and reproducible. Moreover, they are not specific to one species.

We are aware that the industry Task Force has submitted a position paper describing the eye malformation incidents as rabbit specific. Their hypothesis though it's not supported by the evidence for the following reasons:

- The Task Force refers to two developmental toxicity studies in rats (OECD 414, 2010; EOGRTS, 2021) to claim that eye malformations have not been observed in rats. However, peculiarly in these studies that the Task Force indicates, either ophthalmological analysis was not performed at all (2010), or although eye samples were collected, the data were not properly reported (some eye malformations were reported in high dose exposure, see below). Therefore, the reason no adverse effects were observed is because they weren't measured.
- As correctly stated by the dossier submitter, two additional repeated dose toxicity studies in rats (WuXi AppTech, 2019; Bayer CropScience, 2007), clearly indicate eye malformations in rats following TFA exposure (section 10.12 table 17). Therefore, eye malformations following TFA exposure are not rabbit specific.
- Two older repeated dose toxicity studies of 4 and 5 months in rats (USSR,1964) following TFA exposure via inhalation, carried out ophthalmoscopic examination and reported "*severe signs of irritation of the respiratory pathway and of the eyes*" indicating that the eye might be a target tissue of TFA in rats.
- The mechanism of action proposed by the Task Force would hypothetically support the triggering of adverse effects in the eye of rabbit foetuses (because of lactate inhibition and TFA acidification in the eye) at the high exposure level (750 mg/kg), when internal TFA levels are high enough to compete with MCT-1, and trigger the proposed pathway. However, eye malformations in foetuses were observed across lower exposure levels, as we can see from the two DevTox studies in rabbits, including as low as 60mg/kg exposure. Therefore, this mode of action hypothesis is not supported by the evidence.
- The MCT-1 study submitted by the Task Force shows that TFA activates MCT-1 in humans.

It is important to note that skeletal malformations were observed alongside eye defects in developing rabbit foetuses. In the 2024 rabbit DevTox study, skeletal adverse effects

(Sternebrae fused/partially fused) were observed at low medium dose of 60 mg/kg and even at low dose of 30 mg/kg (ribs fused/partially fused). Therefore, no NOAEL can be established for skeletal malformations. Similar skeletal malformation following TFA exposure were also observed in the rat developmental toxicity study, at 150 mg/kg exposure, indicating these are not rabbit specific.

We agree with the dossier submitter's conclusion on the developmental toxicity of TFA and recommend the following additional elements be included in the CLH report:

- In the 2021 EOGRTS (OECD TG 443) in rats, although eye samples were fixed, full results were not reported. However, the study report notes three animals from high dose females (248 mg/kg bw/day, F1 Cohort 1A) that showed retinal rosettes/folds, further supporting the non-rabbit-specific nature of these effects.
- In the developmental toxicity study in rats (2010) the reporting table does not mention the skeletal malformations that were observed at 150 mg/kg
- In the 2024 DevTox study, there is an additional adverse effect missing: there was also a foetus with small lens at 60 mg/kg exposure (118/219 animals were examined at this dose, at higher doses only 101 or 93 were examined). Therefore, the NOAEL for eye malformations should be 30 mg/kg.

10.12 Specific target organ toxicity-repeated exposure

The study WuXi AppTech, 2019 (TG 452) appears to be the same study cited by UBA [see: https://www.umweltbundesamt.de/sites/default/files/medien/421/dokumente/ableitung_eines_gesundheitlichen_leitwertes_fuer_trifluoressigsaeure_fuer_uba-homepage.pdf]. However, key data are missing from the CLH report and reporting table. According to UBA (who has full access to the report), this 1 year repeated dose study in rats with TFA (30, 120, 600 ppm), showed a dose-dependent increase of the enzyme ALT (alanine aminotransferase), an indicator of liver toxicity). Based on these findings, the NOAEL was determined to be 30 ppm, equivalent to 1.8 mg/kg bw/d.

Currently, the reporting table shows that the NOAEL in this study is 600ppm, which is incorrect. ALT is a parameter that has been altered by TFA exposure in other studies too (EOGRTS, 2021; 90-d repeated dose toxicity TG 408, 2007;28-d TG 407, 2014), as shown in the CHL report. Therefore, it's important to include the full findings of the WuXi AppTech, 2019 (TG 452) that the correct NOAEL is 30ppm, which is equal to 1.8 mg/kg, and not 600 ppm.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

11.4 persistent, mobile and toxic (PMT) or very persistent, very mobile (vPvM) properties under CLP Annex I, 4.4

We agree with the classification of TFA as both **PMT and vPvM**, based on the available evidence, as TFA fulfils all the requirements to be placed under these hazard classes.

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Pesticide Action Network (PAN Europe) is a network of NGOs working to reduce the use of hazardous pesticides and have them replaced with ecologically sound alternatives. We work to eliminate dependency on chemical pesticides and to support safe sustainable pest control methods. Our network brings together over 45 consumer, public health and environmental organisations and women's groups from across Europe.