Generations Futures's comments on harmonised classification proposal for the substance trifluoroacetic acid

General comments

Generations Futures welcomes the opportunity to comment the classification proposal for the substance Trifluoroacetic acid (TFA)

We fully support the classification of TFA as a substance with the newly added or adjusted properties of being Reprotoxic 1B, PMT, vPvM, Acute Tox (3).

We also want to highlight that, currently, no data is available on carcinogenicity. Considering the omnipresence of TFA in the environment and the resulting chronic exposure of humans, carcinogenicity data on TFA must be produced and subjected to a harmonized classification procedure when available.

Specific comments regarding reproduction

- **Adverse effects on development**

Clear evidence of foetal eye malformations were observed in two prenatal developmental toxicity studies (PNDTS) performed on rabbits. In both studies, multiple folded retina and absent aqueous/vitreous humour were observed in foetuses.

In the first study (Covance Laboratories, 2021b), multiple folded retinas were observed in all doses (from 180 mg/kg bw to 750 mg/kg bw) in a dose-response manner (0/150 foetuses in 0/18 litters in control; 1/158 foetuses in 1/21 litters at low dose; 5/173 foetuses in 4/24 litters at mid dose; 9/140 in 8/23 litters at high dose). Moreover, absence of the aqueous/vitreous humour was observed in all dose groups (0/150 foetuses in 0/18 litters in control; 1/158 foetuses in 1/21 litters at low dose; 6/173 foetuses in 4/24 litters at mid dose; 8/140 in 6/23 litters at high dose)

In the second study (Labcorp Laboratories, 2024c), multiple folded retina and absent aqueous/vitreous humour were observed for the higher mid dose (250 mg/kg bw) and for the high dose (750 mg/kg bw)

These eye malformations observed are sufficient to classify TFA as a reprotoxic of category 1B for the following reasons:

- The adverse effects observed in the 2 studies (performed in two different laboratories) are very consistent: the same malformations were observed (multiple folded retina and absent aqueous/vitreous humour)
- The effects were dose dependant and a clear relation dose-effect was observed in the two studies
- The incidence of the malformations observed were above the historical control data range of the 2 laboratories
- The malformations occurred in absence of major maternal toxicity
- These adverse effects observed can be considered as significant irreversible toxic effects (eye malformations)
- The 2 studies are of good quality without major deviations from the OECD 414 protocol

Moreover, we strongly oppose the doubts expressed by certain actors aimed at disqualifying the Repro 1B classification proposal, as they claim that the observed effects are not relevant to humans. The CLP regulation states that "*when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate*". However, the information provided by the applicant regarding the mechanism of action does not demonstrate that the effects observed in studies on rabbits would not be relevant to humans.

Finally, as mentioned by the dossier submitter, other supportive evidences is available and in the repeated dose toxicity studies ((Bayer CropScience, 2007; WuXi AppTech, 2019) the eye has been identified as being a target organ also in adult rats after chronic oral exposure.

In conclusion, a classification of TFA as a reprotoxic for the development of category 1B is warranted.

Specific comments regarding Specific target organ toxicity-repeated exposure (STOT-RE)

We agree with the dossier submitter proposal (no classification is warranted).

However, we disagree with the conclusion of the dossier submitter regarding the 1-year repeated-dose oral toxicity study (WuXi AppTech, 2019). The dossier submitter concludes that the NOAEL is equal to 600 ppm (males: 37.8 mg/kg bw/d; females: 64.0 mg/kg bw/day). However, after an in-depth analysis of the raw data of this study, the German agency UBA concluded to a NOAEL equal to 30 ppm (1.8 mg/kg bw in males). The critical effect identified by UBA was the increase of the ALT enzyme at 120 ppm and 600 ppm. Therefore, the NOAEL in this study is 30 ppm.

Please refer to this document: https://www.umweltbundesamt.de/sites/default/files/medien/421/dokumente/ableitung_eines_gesundheitlichen_leitwertes_fuer_trifluoressigsaeure_fuer_uba-homepage.pdf

Specific comments on PMT and vPvM properties

The data are unanimous regarding the persistence of TFA : there is no degradation observed in the different relevant studies. We agree with the dossier submitter to conclude with a high degree of certainty that TFA- must be considered as meeting the “persistent” (P) and “very persistent” (vP) criteria for the three compartments studied: freshwater, freshwater sediment and soil.

Regarding mobility, TFA is fully miscible with an extremely low adsorption potential. When log Koc values could be calculated with OECD TG 106, the lowest log Koc values are less than 2 (-2.02 and 1.27). Moreover, lysimeter studies provided in the regulatory dossier of the pesticide active substances flufenacet and fluopyram confirm the very high mobility of TFA. In addition, monitoring studies worldwide provide further evidence of the persistent and mobile, indicating the presence of TFA in surface waters and ground water as well as drinking water across Europe. We agree with the dossier submitter to conclude with a high degree of certainty that TFA- must be considered to fulfil the “mobile” (M) and ‘very mobile’ criteria (vM).

As explained before, there is sufficient evidence for classifying TFA as reprotoxic for the development of category 1B. The T criterion is therefore met.

In conclusion, TFA meets the criteria for persistence, mobility and toxicity and must be classified as PMT and vPvM.

On behalf of Générations Futures,

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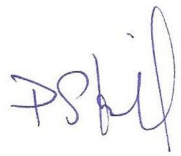

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