TFA
Trifluoroacetic acid
Task Force

28 02 2024

SUBJECT: TRIFLUOROACETIC ACID (TFA) – UPDATE TO NOTIFICATION UNDER ARTICLE 56 OF REGULATION (EC) NO 1107/2009

To whom it may concern,

On behalf of the TFA Task Force (TF) members which market pesticides in EU – BASF, Bayer, Corteva, Syngenta – we would like to provide a further update following the original notification by Bayer on January 7th, 2021, as updated by Bayer on November 30th, 2021, on the subject of trifluoroacetic acid (TFA) concerning relevant information according to Art. 56 of Regulation (EC) No 1107/2009.

As background information, the REACH lead registrant for TFA, a producer of TFA and member of the Task Force, was requested by the European Chemicals Agency (ECHA) to provide, in addition to the submitted toxicological data package included in the REACH registration dossier, an Extended one-Generation Reproductive Toxicity Study (EOGRTS) in rats and a Developmental Toxicity (DevTox) study in rabbits.

The results of the DevTox study (Renault, R. 2021a) in rabbits revealed a higher incidence of major fetal abnormalities predominantly affecting the eyes. Since no comparable fetal findings were observed in previous developmental toxicity studies in rats conducted at comparable dose levels (Baxter, G. E., 2010; and Wei, Ch., 2020), the findings may be rabbit specific. This is further supported by the EOGRTS with sodium trifluoroacetate in rats (Renault, R. 2021b) which does not show any TFA treatment related developmental toxicity. Therefore, to fully understand the relevance of these findings, the TFA TF considered it necessary to conduct follow-up studies with the aim to clarify species differences, to determine the mode-of-action (MoA) and to establish a No Observed Adverse Effect Level (NOAEL). These studies have been agreed to and authorized by Member State (MS) Poland in line with Directive 2010/63/EU on the protection of animals used for scientific purposes.

Ocular tissues proved to be a major target in a limited number of rabbit fetuses following treatment of pregnant rabbits with high oral doses of TFA as demonstrated by the absence of aqueous and vitreous humor with secondary multiple foldings of the retina. Follow-up assessments, consisting of *in-vitro* and *in-vivo* studies, were conducted to examine species differences, internal exposure and the potential MoA for fetal eye findings.

The results indicate that TFA does not interfere with the retinoic acid pathway, since it neither binds nor inhibits CYP26 (a central enzyme in the retinoic acid pathway) *in-vitro* and had no effect on Vitamin A levels *in-vivo* up to the highest dose tested. An *in-vitro* MCT assay proved that TFA is a substrate of Monocarboxylate Transporters (MCTs) that are essential amongst others for lactate, energy and water homeostasis in eyes. After high doses of TFA to pregnant rabbits excessively high internal exposure concentrations were observed in maternal animals and fetuses that ranged at or even exceeded the concentration required to attain the EC50 of 12 mM at MCT transporters. This was accompanied with particularly high rabbit eye aqueous/vitreous humor concentrations of TFA in samples from pregnant rabbits and fetuses. TFA is known for its chaotropic properties, which could affect protein integrity at elevated concentrations leading to impairment of the development of the vitreous body. Overall, a threshold based mechanism is suggested for triggering a disruption of vitreous body structures and for

relevant inhibition of MCT transporters in ocular tissues. (Details are provided in the Annex 2.) All study reports are currently under finalization and will be submitted as soon as they become available.

Following the completion of the follow-up studies in which a NOAEL was derived, the generic risk assessment was updated with TFA. The results indicate that when applying appropriate assessment methods to all available drinking water and dietary monitoring data, there is no risk for humans associated with the short- and long-term intake of residue of TFA, independent from the precursor substances and natural sources. Therefore, related potential harmful effects from TFA are not to be expected. This updated assessment is in agreement with the conclusions drawn in Solomon *et al.* 2016. In addition, a health-based drinking water limit value for TFA of 290 µg/L is proposed following the WHO Guidelines for drinking-water quality. An EU wide harmonized health-based drinking water guidance value for TFA, a ubiquitous compound, is required.

In November 2022, ECHA notified the REACH lead registrant and the competent EU and national authorities that it had completed its REACH dossier evaluation process - taking into account the scientific information included in the REACH dossier as updated in July 2022. Based on the review of the updated REACH dossier ECHA considered TFA a possible candidate for a proposal for harmonised classification and labelling (CLH) according to Article 37 of Regulation (EC) No 1272/2008 ("CLP"). On 28 November 2023, Germany has released its intention for a revised harmonized classification, with 31 May 2024 as indicated submission date to ECHA. The REACH lead registrant has provided an update to the REACH dossier around the same time of this Art.56 update that includes a self-classification proposal by the lead registrant.

The Standing Committee on Plants, Animals, Food and Feed (SCoPAFF) on 24/25 May 2023 discussed and reflected on TFA as a common metabolite as recorded in the meeting minutes (sante.g.3(2023)8536936), where "*One Member State asked how any new data on TFA, that may be submitted in dossiers for renewal of approval of active substances, would be handled in view of avoiding duplication of work. The Commission indicated it would further reflect on it, also with EFSA, in view of ensuring a pragmatic and manageable approach.*" In light of this discussion, the TFA TF proposes that, for efficiency reasons, a stand-alone assessment is conducted at EU level for TFA as a common metabolite of a number of pesticide active substances (ASs) under Regulation (EC) No 1107/2009 in parallel to the harmonised CLH process according to Regulation (EC) No 1272/2008. Exposure data of TFA as a degradation product of pesticides are specific to individual pesticide active substances and may be assessed as part of the respective approval or renewal procedure separately.

This submission is made at the same time to EFSA, EU Commission (DG SANTE) and the authorities of all EU Member States, Great Britain and Northern Ireland, Norway and Switzerland.

[redacted]

Yours sincerely, For and on behalf of TFA TF

[redacted]

[redacted]

Attached:

Annex 1 – Developmental toxicity evaluation of TFA: study summaries;

Annex 2 –TFA mode-of-action paper for eye findings;

Annex 3 - TFA Developmental Toxicity Studies - BMD Report for eye findings;

Annex 4 – Updated generic risk assessment (not specific to a certain precursor substance);

Annex 5 – Proposal of a health-based drinking water limit value for TFA;

Annex 6 – Position paper RSA.

References

Baxter, G. E.2010, Trifluoroacetic acid: Embryo-fetal oral gavage toxicity study in rats, unpublished report No 09-4352, GLP, 2010-11-08.

Renault, R. 2021a; Sodium trifluoroacetate: Study for effects on embryo-fetal development in the New Zealand white rabbit by oral gavage administration, Study number 8437242, GLP, 2021-10-27.

Renault, R. 2021b; Sodium Trifluoroacetate: Extended One Generation Reproductive Toxicity Study in the Han Wistar Rat by Dietary Administration, Study number 8439567, GLP, 2022-03-11.

Wei Ch. 2020 ; Prenatal Developmental Toxicity Study of TFSK TFAK REACTION MASS following Oral Administration to Pregnant Rats by Gavage, Report no: G1963B0020. Study number: GP190132, GLP, 2020-08-24.

Solomon K, Velders G, Wilson S, Madronich S, Longstreth J, Aucamp P, Bornman J. 2016. Sources, fates, toxicity, and risks of trifluoroacetic acid and its salts: Relevance to substances regulated under the Montreal and Kyoto protocols. A report prepared by the UNEP Environmental Effects Assessment Panel and published in the Journal of Toxicology and Environmental Health B. published by Taylor & Francis in J Toxicol Environ Hlth B on June 27, 2016, available online: http://www.tandfonline.com/10.1080/10937404.2016.1175981

Renaut, R. (2024a) - Sodium Trifluoroacetate: Proof of Concept Study in the Rabbit by Oral Gavage Administration; Labcorp Study No 8485227; non-GLP, unpublished; 2024-xx-xx DRAFT Report

Renault, R. (2024b) - Sodium Trifluoroacetate: Toxicokinetic and Dose Range Finding Study for Effects on Embryo-Fetal Development in the New Zealand White Rabbit by Oral Gavage Administration; Labcorp Study No 8485228; non-GLP, unpublished; 2024-xx-xx DRAFT Report

Renault, R. (2024c) - Sodium Trifluoroacetate: Study for Effects on Embryo-Fetal Development in the New Zealand White Rabbit by Oral Gavage Administration; Labcorp study no. 8485229; GLP, unpublished, 2024-xx-xx DRAFT report

Bender, E., (2023) Sodium Trifluoroacetate – Evaluation in the in vitro MCT-1 assay, non-GLP; unpublished report M-848417-01-1; 2023-11-29

Ongeri, L. (2021) - A study to assess the binding and inhibition of recombinant human CYP26 (ALL-trans- -RETINOIC ACID MONOXYGENASE) by test item; CLS Study No O-26990; non-GLP, unpublished; 2021-12-17