**Supplement to “Pressurized metered-dose inhalers using next-generation propellant HFO-1234ze(E) deposit negligible amounts of trifluoracetic acid in the environment”**

By

Shivendra G. Tewari1,\*, John P. Bell2, Nigel Budgen3, Stefan Platz4, Megan Gibbs1, Peter Newham4, Holly Kimko1

1Systems Medicine, Clinical Pharmacology & Safety Sciences, R&D BioPharmaceuticals, AstraZeneca, Gaithersburg, MD, US

2BioPharmaceuticals Medical, AstraZeneca, Baar, Switzerland

3Global Safety, Health and Environment, AstraZeneca, Macclesfield, UK

4Clinical Pharmacology & Safety Sciences, R&D BioPharmaceuticals, AstraZeneca, Cambridge, UK

Running Head: Novel pMDIs lead to negligible rainwater TFA

\*Address correspondence to: shivendra.tewari@astrazeneca.com

**Text S1: Atmospheric conditions used for calculating the yield of trifluoroacetic acid from HFO-1234ze(E)**

Figure S1 shows the proposed atmospheric-degradation routes of HFO-1234ze. In our box-model of HFO-1234ze degradation, there are total twenty-nine chemical species, of which twenty chemical species involved in the HFO-1234ze degradation route (Fig. S1). In our simulations, we have not assumed dispersion of the chemical species outside of the box. To avoid build-up of chemical species to unrealistic values, we have done the following: *i*) fixed the concentration of H2 (550 ppb), O3 (30 ppb), and CO (120 ppb) throughout the simulation, *ii*) assumed mass conservation of NOx family, i.e., NO, NO2, NO3, and N2O5, and *iii*) added nine chemicals to maintain “steady-state” conditions in each diurnal cycle. We used the initial concentrations of OH, NO, NO2, and HO2 species at different altitudes as reported by Reifenberg et al. [1], displayed in Figures S1. To accurately estimate the time-duration of HFO-1234ze degradation, we included diurnal variation of NO, NO2, OH, and HO2 species in the model by using the NCAR-TUV radiation model available in Framework for 0-D Atmospheric Modeling (F0AM) [2], which incorporates the effect of sun-zenith angle, altitude, ozone column, and albedo on the photolysis rates (J-values). For sun-zenith angle calculations, we used the location coordinates of Paris, France. Figure S3 shows a representative diurnal cycle of NO, NO2, OH, and HO2.

A diagram of a chemical reaction

Description automatically generated

**Figure S1**. Atmospheric reactions involved in degradation of HFO-1234ze (E-CF3CH=CHF). The black arrows indicate the chemical reactions included in the box model, and the blue arrows indicate reactions not included in our model calculations. The chemical highlighted red is trifluoroacetic acid, CF3C(O)OH.

A graph of different molecules

Description automatically generated with medium confidence

**Figure S2**. Concentrations of NO, NO2, OH, and HO2 species, reported in Reifenberg et al. [1], averaged over Europe as a function of atmospheric pressure.

A graph of different types of data

Description automatically generated with medium confidence

**Figure S3.** A representative diurnal variation in NO, NO2, OH, and HO2 concentration at the ground level using Paris location coordinates. All chemical species are in the unit of parts-per-billion (ppb).

**References**

1. Reifenberg, S.F., et al., Numerical simulation of the impact of COVID-19 lockdown on tropospheric composition and aerosol radiative forcing in Europe. Atmospheric Chemistry and Physics, 2022. 22(16): p. 10901-10917.

2. Wolfe, G.M., et al., The Framework for 0-D Atmospheric Modeling (F0AM) v3.1. Geosci. Model Dev., 2016. 9(9): p. 3309-3319.