Sevoflurane: Impurities and Stability Testing

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SUPPLEMENTARY MATERIAL

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1. Materials and methods

Figure S1. Analyzed Sevoflurane formulations, **batch-1** samples.

Humidity Chamber HCP 108		
Stainless steel interior (deep-drawn, electropolished)	Volume (L)	108
	Width / Height / Depth (**mm**)	560 / 480 / 400
Ventilation	Uniform atmosphere and temperature distribution through enclosed non-turbulent ventilation system, fully covered by the sterilization process.	✓
Temperature	Electronic microprocessor temperature controller with Pt100 and auto-diagnostic system.	✓
	Temperature sensors Pt100 Class A in 4-wire circuit for uninterrupted operation on failure of one Pt100 with warning indication.	double
	Temperature range with humidity control (°**C**).	from 20 up to 90
	Temperature range without humidity control(°**C**)	from 20 up to 160
	Temperature variation in time (to DIN 12 880: 2007-05) (°**C**)	≤ ± 0.1
	Temperature uniformity in chamber at 50 °C (to DIN 12 880:2007-05) (°**C**)	≤ ± 0.3
Humidity	Capacitive humidity sensor	✓
	Accuracy of the humidity sensor (%)	1
	Humidity range (%)	From 20 up to 95
	Accuracy of setting (%)	1
	Humidity variation in time	± 1 % RH max

Figure S2. Memmert Humidity Chamber (HCP108) used for storage at 40 °C and 75% RH conditions (***aa***) and some technical characteristics of the chamber.

2. Gas Chromatography-Mass Spectrometry (GC-MS): Qualitative and quantitative determination of impurities in SF1, SF2, and SF3.

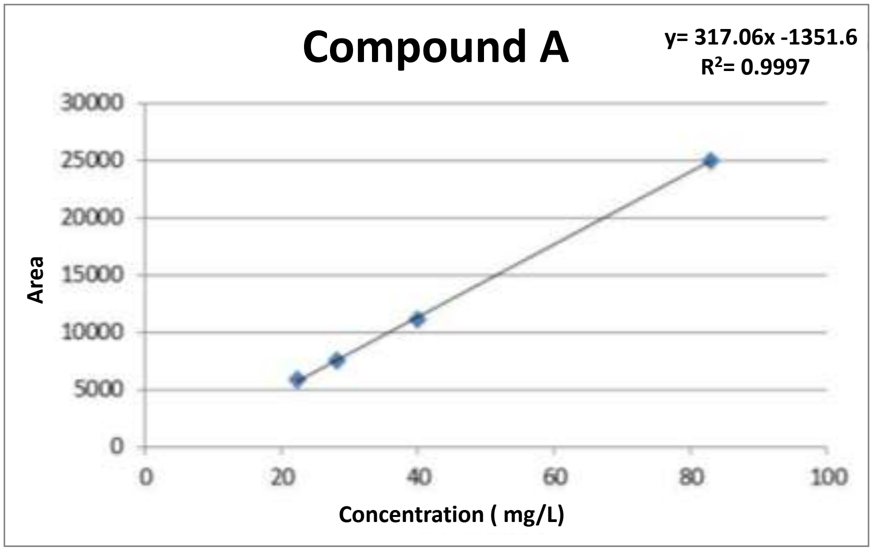

Figure S3. GC-MS Calibration curve for compound **A**.

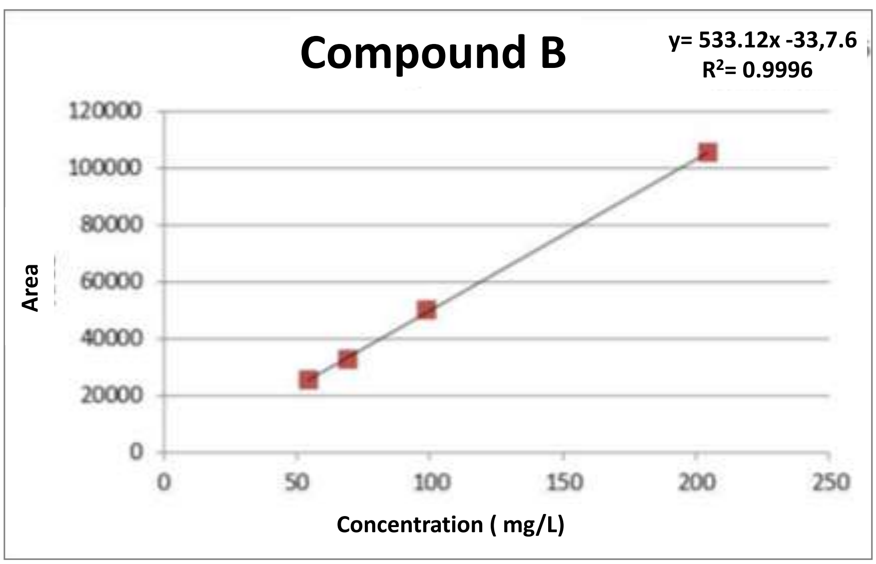

Figure S4. GC-MS Calibration curve for compound **B**.

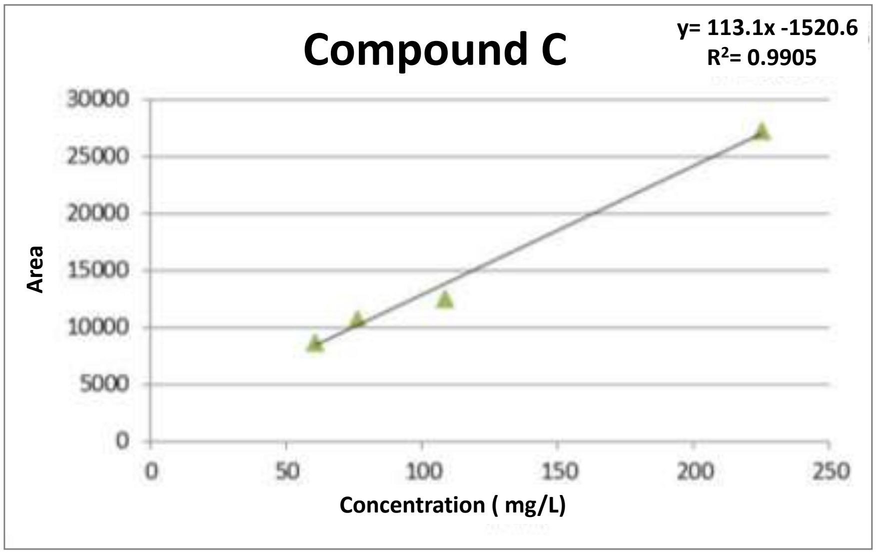

Figure S5. GC-MS Calibration curve for compound **C**.

The contents of **A** – **C** were measured making at least three replicas for each sample.

Figure S6. GC-MS chromatograms of ***SF3_batch-1_t6-std*** (left) and ***SF3_batch-1_t6-aa*** (right).

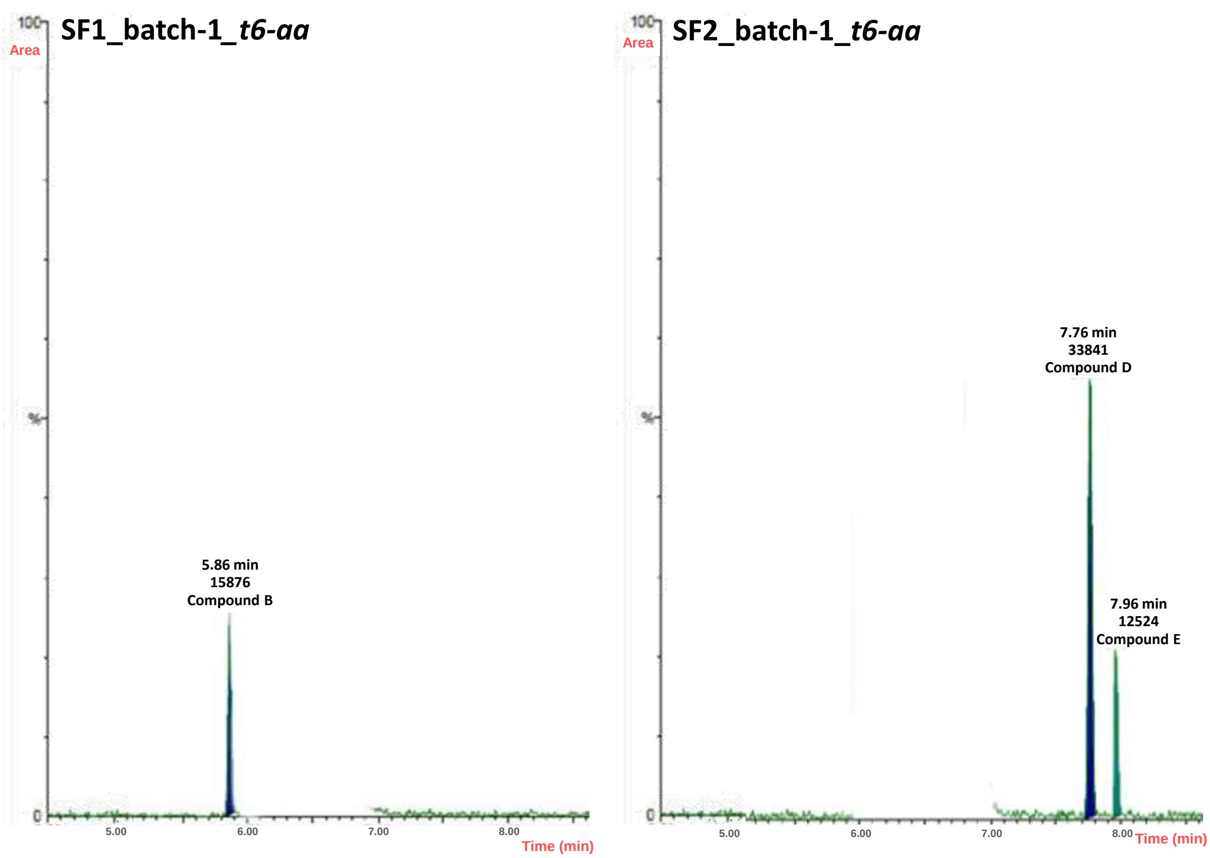

Figure S7. GC-MS chromatograms of ***SF1_batch-1_t6-aa*** (left) and ***SF2_batch-1_t6-aa*** (right).

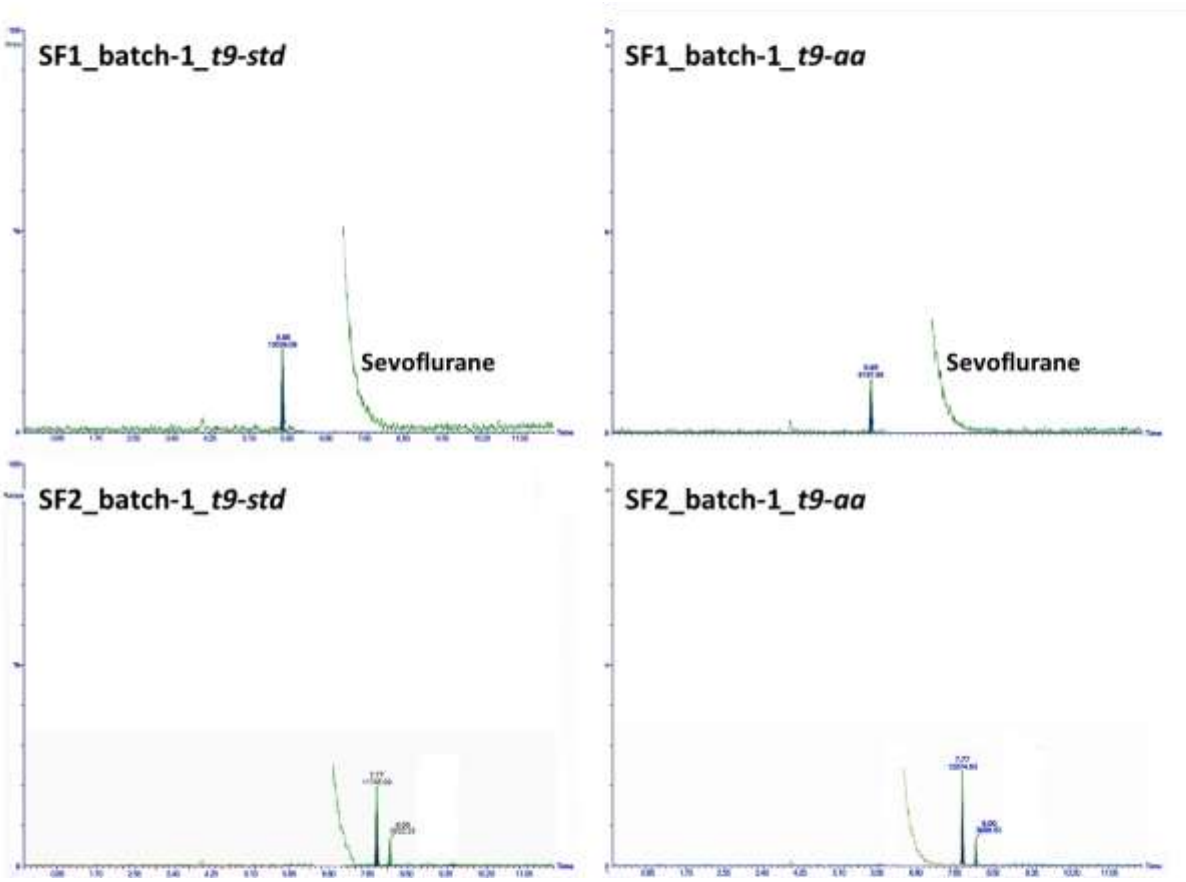

Figure S8. Top: GC-MS chromatograms of **SF1_batch-1_*t9-std*** (left) and **SF1_batch-1_*t9-aa*** (right); Bottom: GC-MS chromatograms of **SF2_batch-1_*t9-std*** (left) and **SF2_batch-1_*t9-aa*** (right).

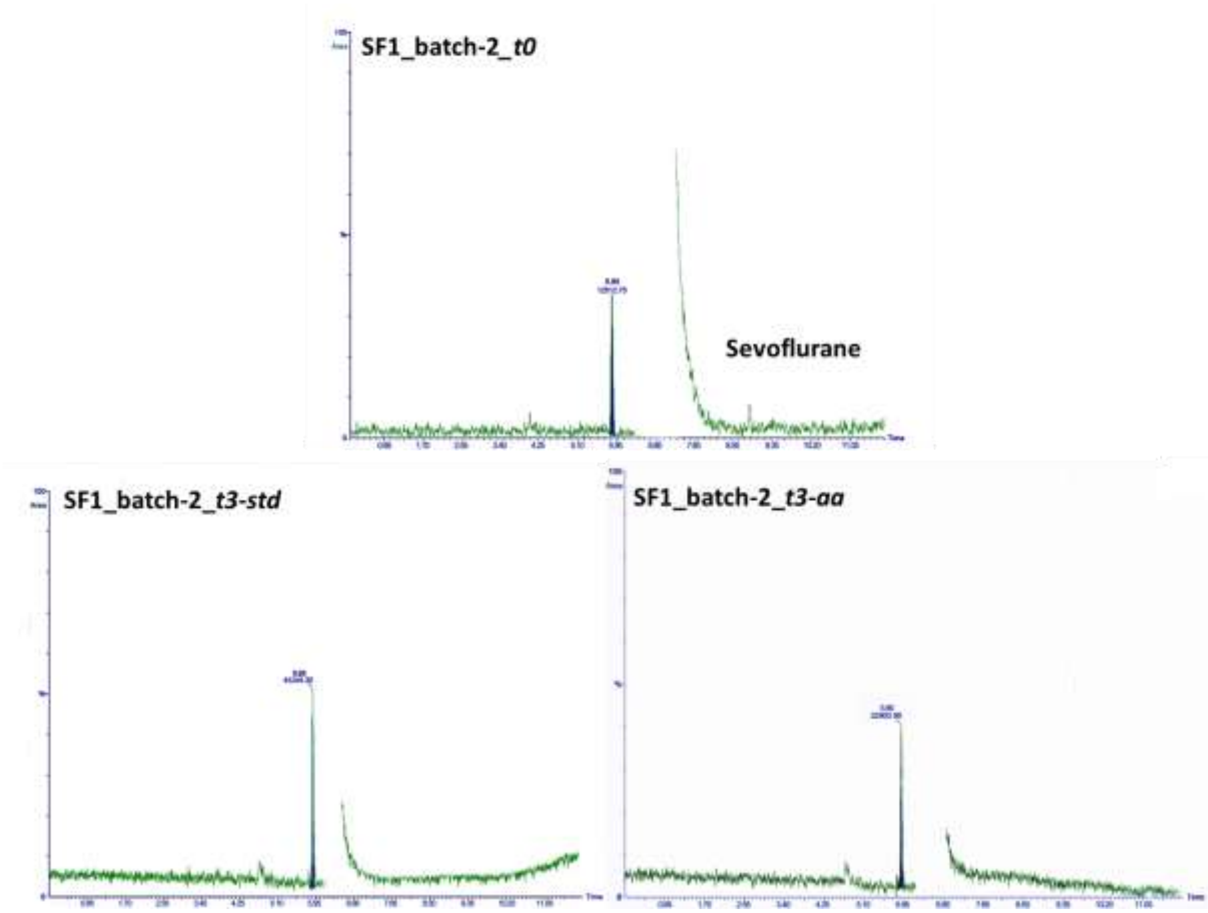

Figure S9. Top: GC-MS chromatogram of **SF1_batch-2_*t0***; Bottom: GC-MS chromatograms of **SF1_batch-2_*t3-std*** (left) and **SF1_batch-2_*t3-aa*** (right).

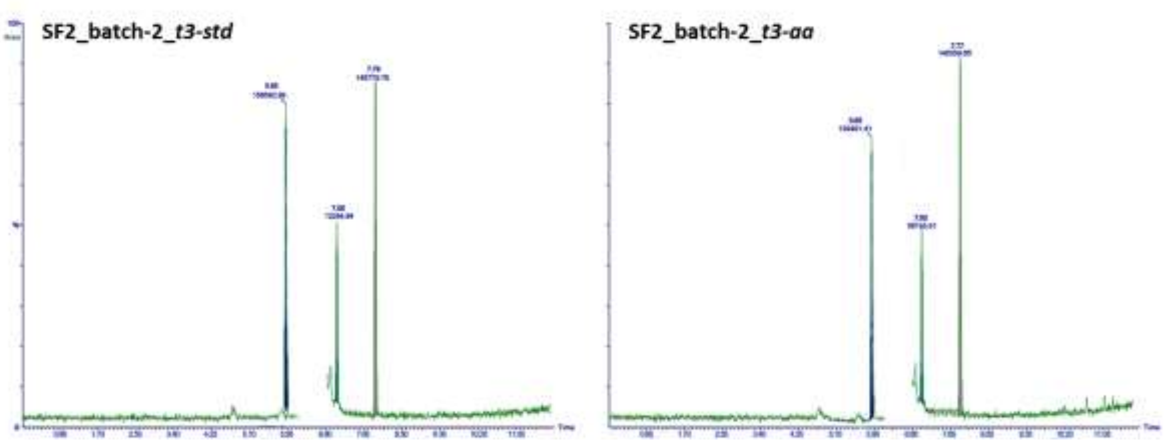

Figure S10. GC-MS chromatograms of **SF2_batch-2_*t3-std*** (left) and **SF2_batch-2_*t3-aa*** (right).

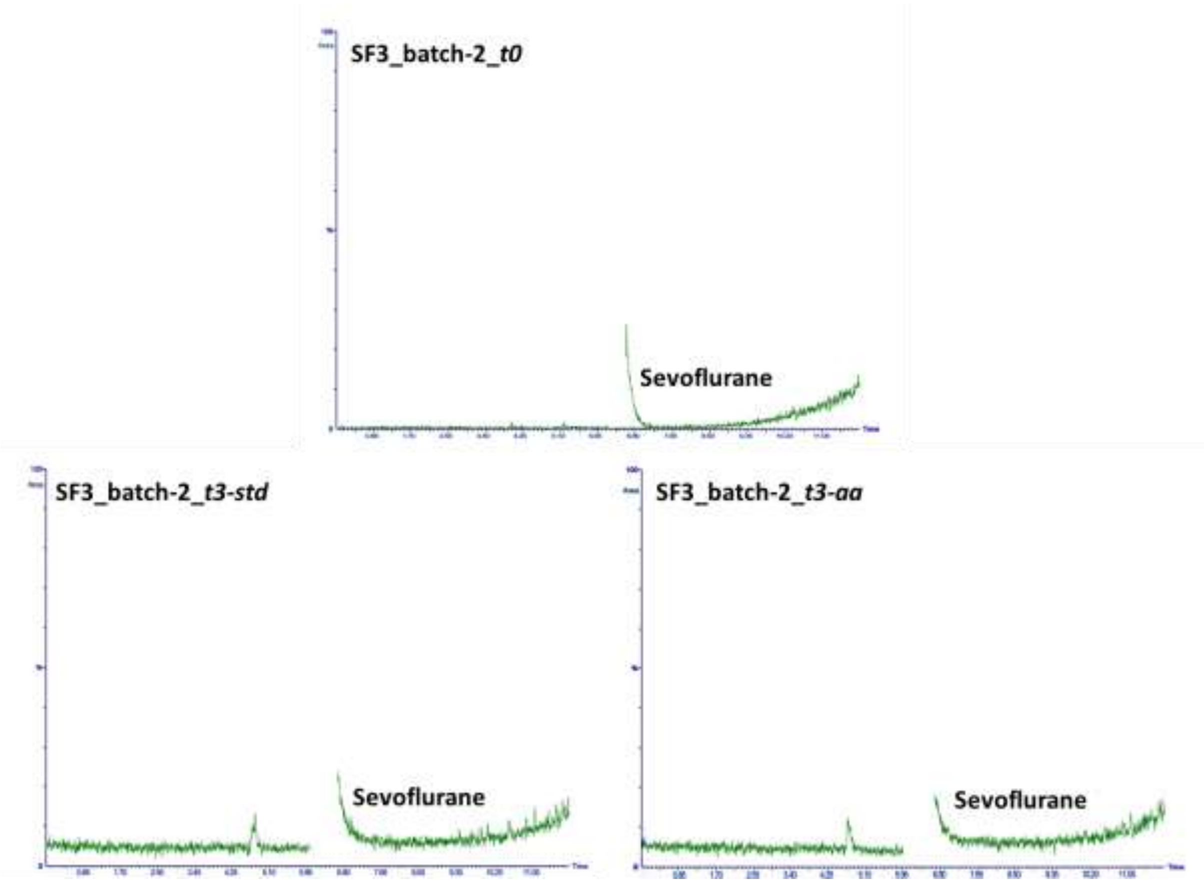

Figure S11. Top: GC-MS chromatogram of ***SF3_batch-2_t0***; Bottom: GC-MS chromatograms of ***SF3_batch-2_t3-std*** (left) and ***SF3_batch-2_t3-aa*** (right).

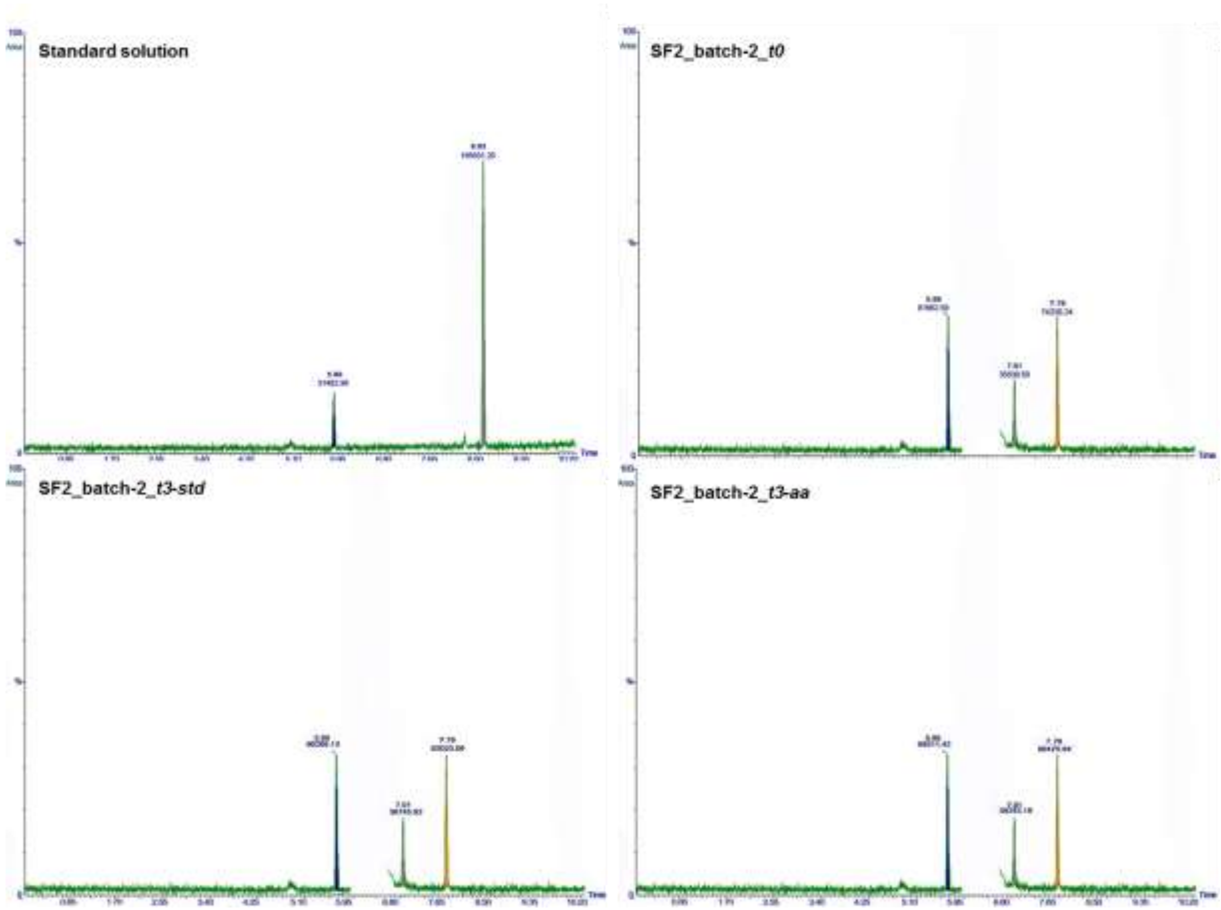

Figure S12. GC-MS chromatograms of: Calibrated standard solution containing impurity **B** and **CSE** (top, left), **SF2_batch-2_*t0*** (top, right), **SF2_batch-2_*t3-std*** (bottom, left), and **SF2_batch-2_*t3-aa*** (bottom, right).

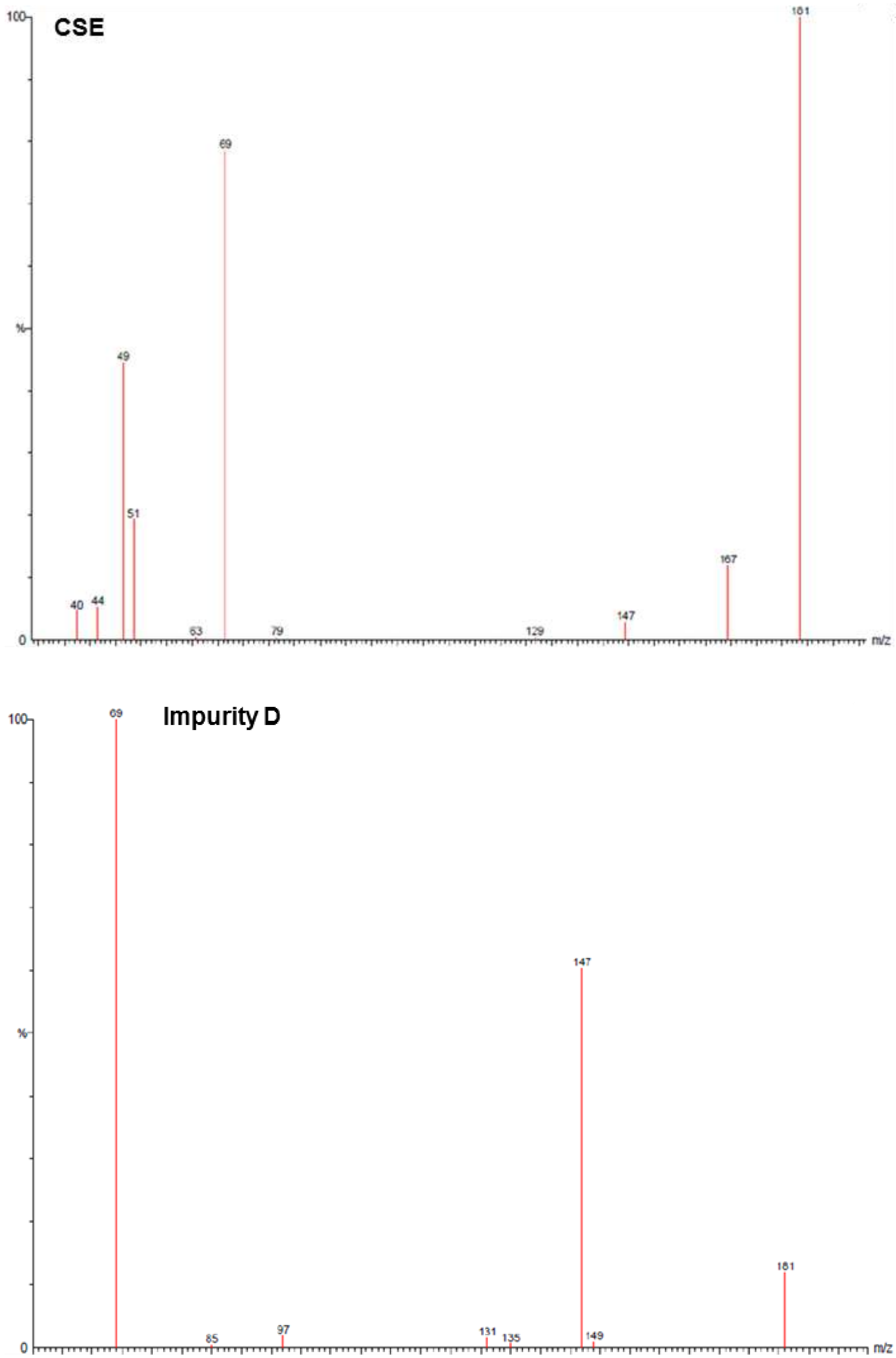

Figure S13. Low resolution MS spectra of **CSE** (top) and impurity **D** (bottom).

3. High-Resolution Mass Spectrometry (HRMS): Identification of impurities in SF2.

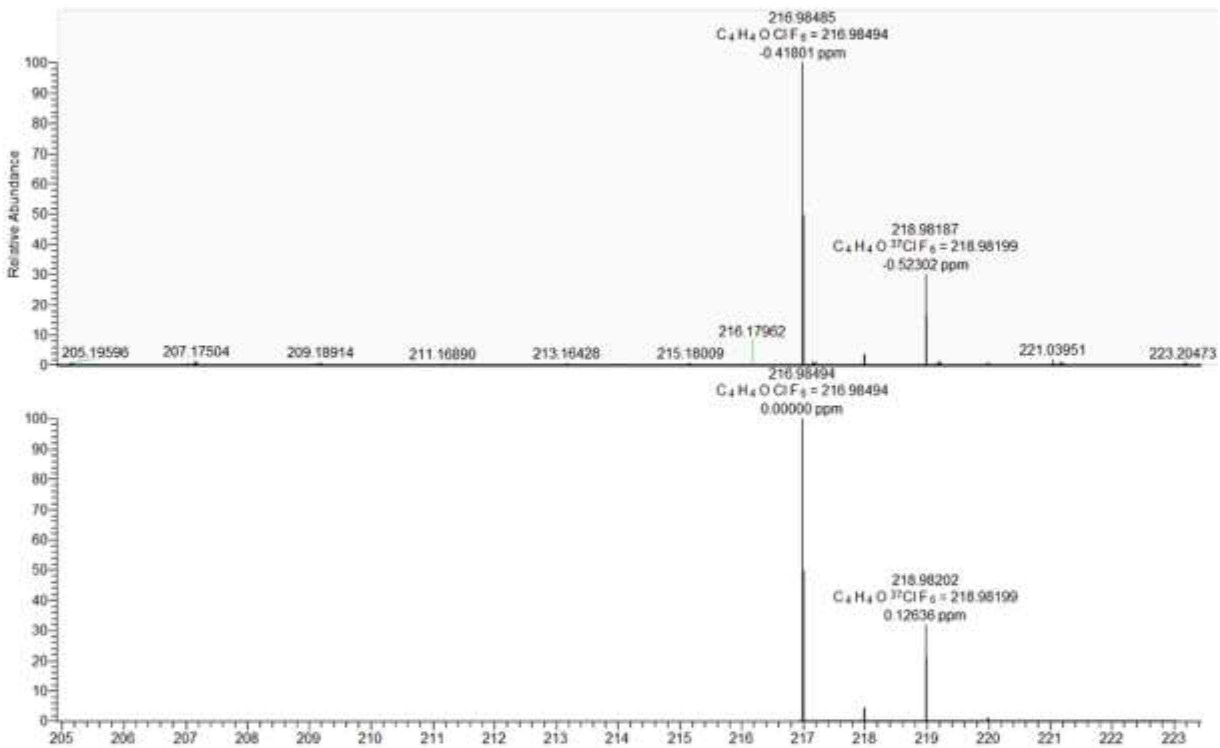

Figure S14. Top: HRMS spectrum of impurity **D** showing molecular peaks after Chemical ionization (CI); Bottom: Theoretical molecular formula and corresponding predicted HRMS peaks.

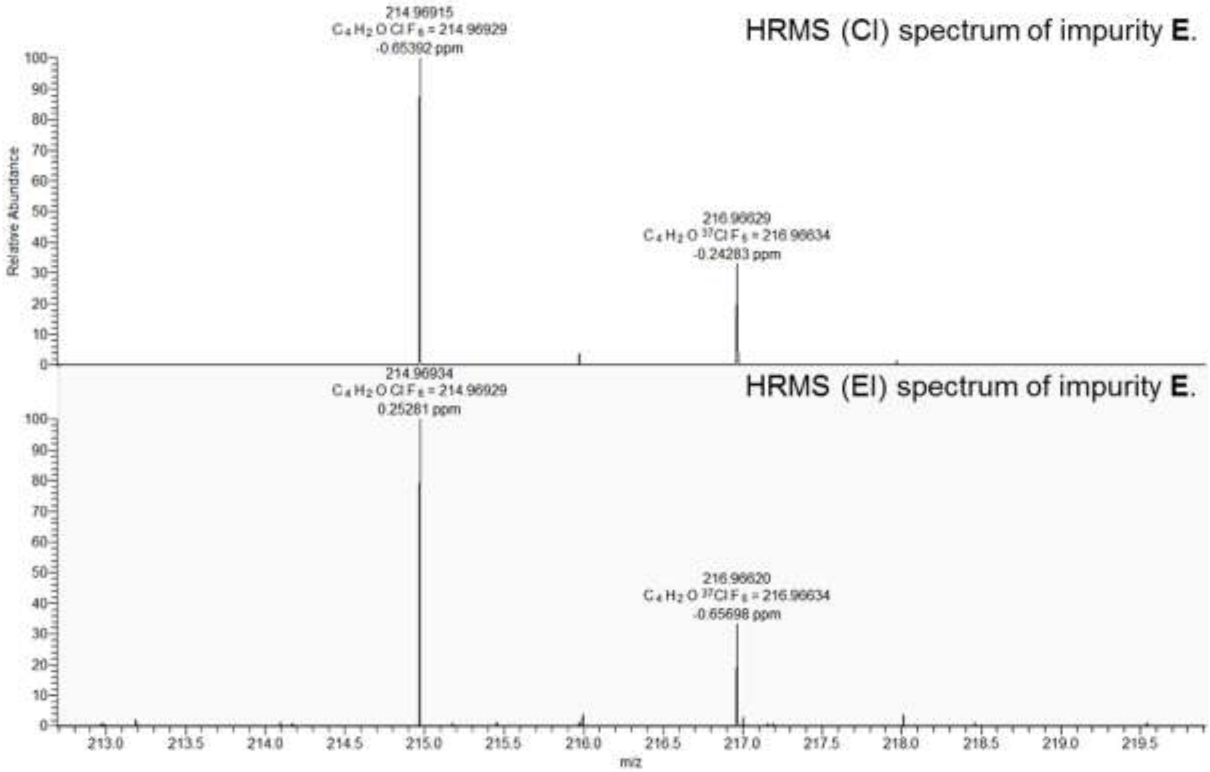

Figure S15. HRMS spectrum of impurity **E** showing molecular peaks after Chemical Ionization (CI, top) and after Electron Impact (EI, bottom).

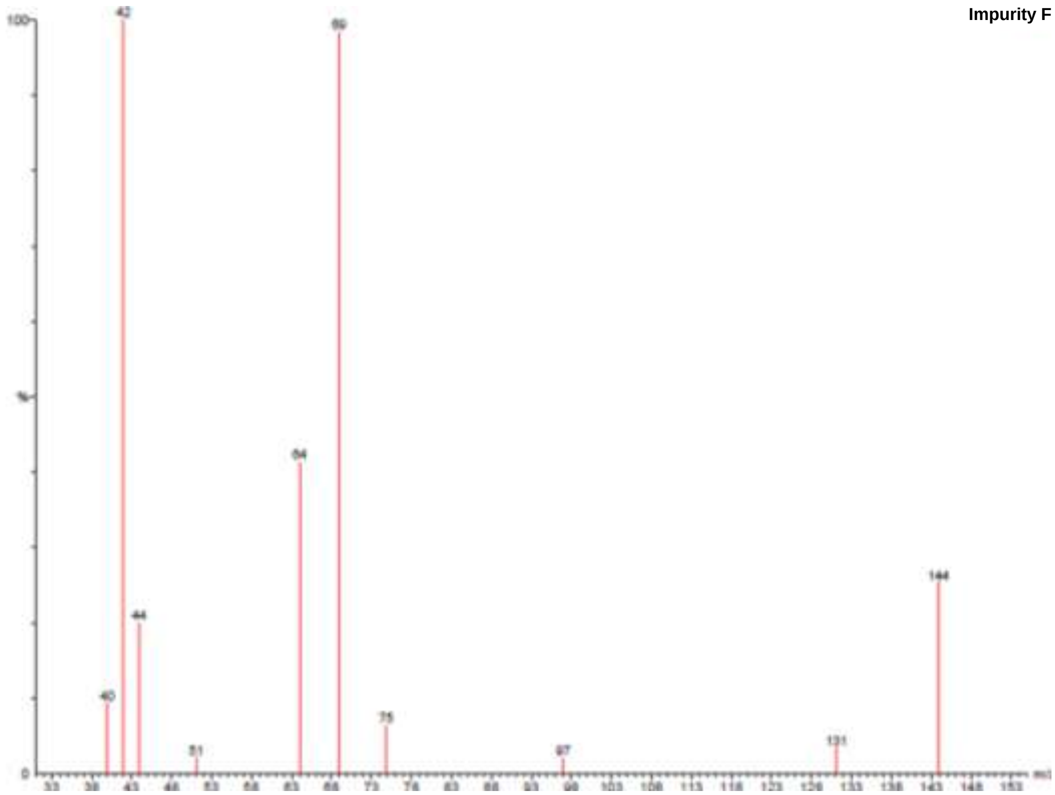

Figure S16. Low resolution MS spectrum of impurity **F**.

4. Ion–Exchange Chromatography analysis: Qualitative and quantitative determination of anions in SF1, SF2, and SF3.

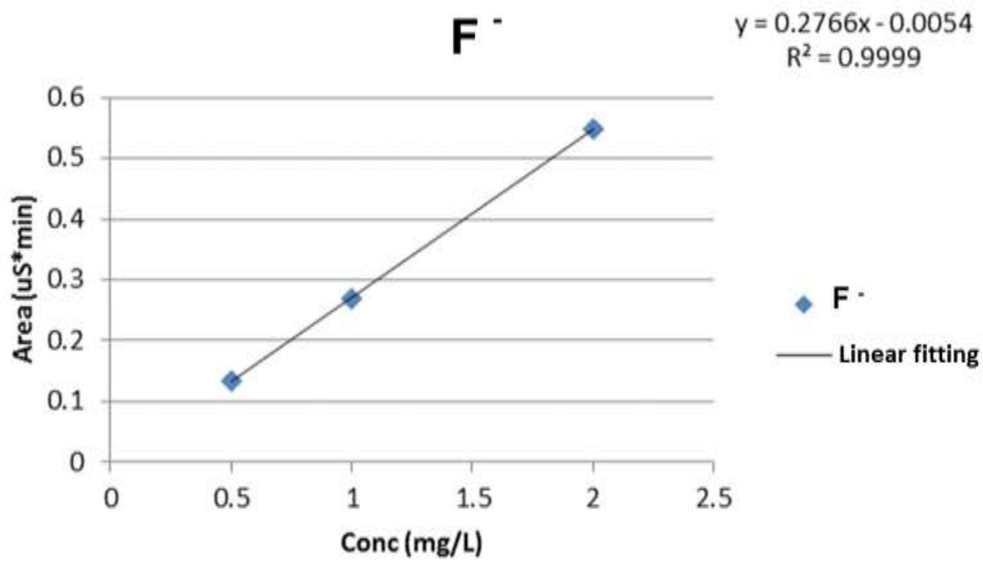

Figure S17. IC Calibration curve for fluoride anions.

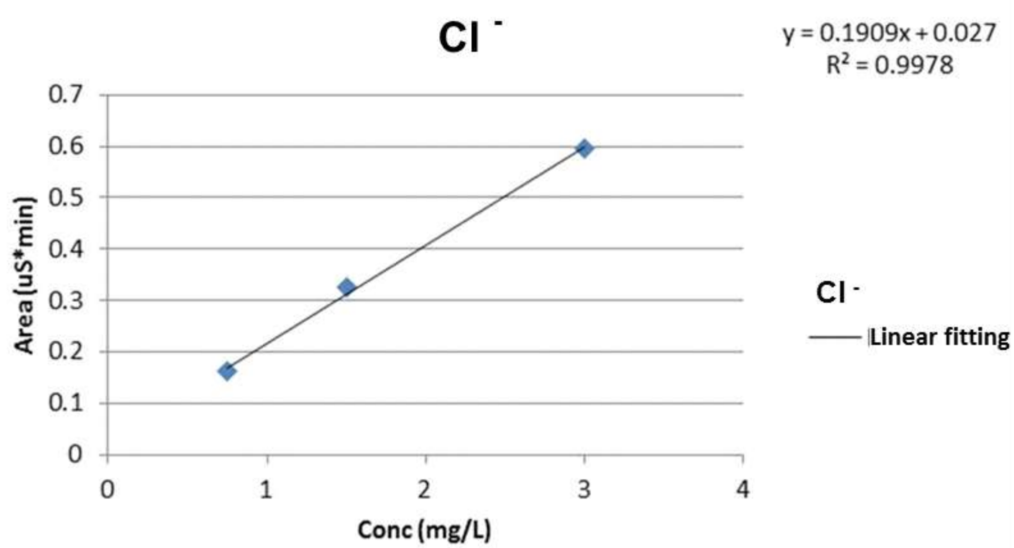

Figure S18. IC Calibration curve for chloride anions.

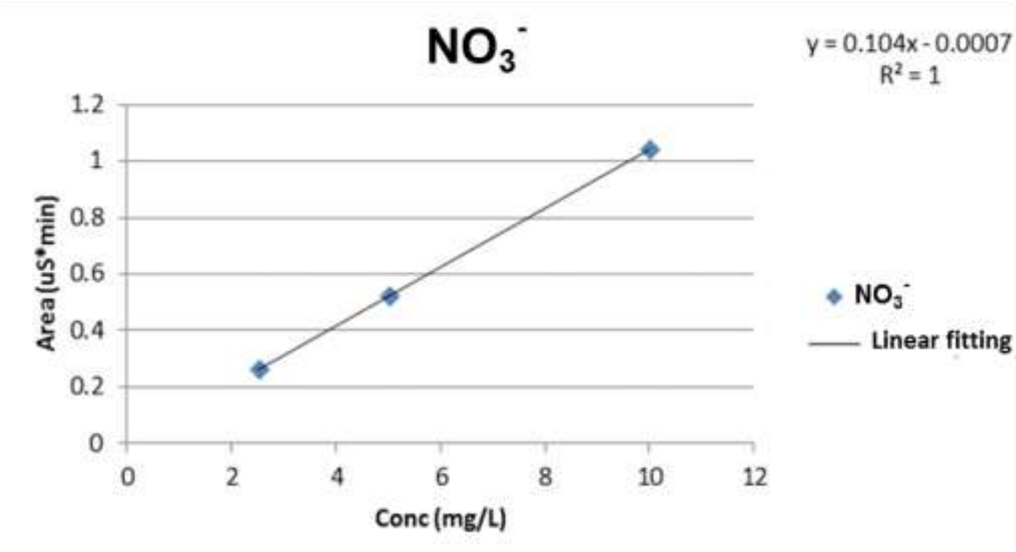

Figure S19. IC Calibration curve for nitrate anions.