AGU PUBLICATIONS

Geophysical Research Letters

RESEARCH LETTER
10.1002/2014GL062785

Key Points:
- Measurements of potent greenhouse gases
- Emissions for the fluranes are increasing
- Halothane declines

Supporting Information:
- Text S1
- Table S1
- Table S2
- Table S3
- Table S4
- Table S5
- Table S6
- Figure S1
- Figure S2

Correspondence to:
M. K. Vollmer,
martin.vollmer@empa.ch

Citation:
Vollmer, M. K., T. S. Rhee, M. Rigby, D. Hofstetter, M. Hill, F. Schoenenberger, and S. Reimann (2015), Modern inhalation anesthetics: Potent greenhouse gases in the global atmosphere, *Geophys. Res. Lett.*, *42*, 1606–1611, doi:10.1002/2014GL062785.

Received 8 DEC 2014
Accepted 9 FEB 2015
Accepted article online 12 FEB 2015
Published online 13 MAR 2015

Modern inhalation anesthetics: Potent greenhouse gases in the global atmosphere

Martin K. Vollmer[1], Tae Siek Rhee[2], Matt Rigby[3], Doris Hofstetter[4], Matthias Hill[1], Fabian Schoenenberger[1], and Stefan Reimann[1]

[1]Laboratory for Air Pollution and Environmental Technology, Empa, Swiss Federal Laboratories for Materials Science and Technology, Dubendorf, Switzerland, [2]Korea Polar Research Institute, KIOST, Incheon, South Korea, [3]School of Chemistry, University of Bristol, Bristol, United Kingdom, [4]Alphacare, Zurich, Switzerland

Abstract Modern halogenated inhalation anesthetics undergo little metabolization during clinical application and evaporate almost completely to the atmosphere. Based on their first measurements in a range of environments, from urban areas to the pristine Antarctic environment, we detect a rapid accumulation and ubiquitous presence of isoflurane, desflurane, and sevoflurane in the global atmosphere. Over the past decade, their abundances in the atmosphere have increased to global mean mole fractions in 2014 of 0.097 ppt, 0.30 ppt, and 0.13 ppt (parts per trillion, 10^{-12}, in dry air), respectively. Emissions of these long-lived greenhouse gases inferred from the observations suggest a global combined release to the atmosphere of 3.1 ± 0.6 million t CO_2 equivalent in 2014 of which ≈80% stems from desflurane. We also report on halothane, a previously widely used anesthetic. Its global mean mole fraction has declined to 9.2 ppq (parts per quadrillion, 10^{-15}) by 2014. However, the inferred present usage is still 280 ± 120 t yr^{-1}.

1. Introduction

Inhalation anesthetics are subject of debate because of their contributions to the greenhouse effect and their potential to destroy stratospheric ozone associated with their long atmospheric lifetimes (Table 1 and references therein). While our understanding of the physicochemical properties of these substances has improved dramatically in recent years, estimates of the quantities emitted to the atmosphere have remained highly speculative [*Langbein et al.*, 1999; *McCulloch*, 2000; *Sulbaek Andersen et al.*, 2010; *Ryan and Nielsen*, 2010; *Ishizawa*, 2011; *Sulbaek Andersen et al.*, 2012a; *Mychaskiw and Eger*, 2013; *Sherman*, 2013; *Sherman et al.*, 2014]. One option for estimating emissions is a "bottom-up" approach (as has so far been done for these anesthetics), in which industrial production and clinical usage figures are combined with assumptions about release factors (for example, application techniques in the operating theater and rates of in vivo metabolism). However, these bottom-up estimates remain inherently uncertain for anesthetics due to producer confidentiality and varying clinical practices both geographically and in time. We present an alternative approach in which we use measured atmospheric abundances and their trends, combined with models of atmospheric transport and chemistry. Such an independent "top-down" approach provides a tool to assess globally integrated emissions as well as regional emission patterns [*Nisbet and Weiss*, 2010; *Weiss and Prinn*, 2011]. This top-down method is particularly suitable for the compounds discussed here, because they are exclusively used in anesthesia, and hence, all emissions can be uniquely attributed to this application. In our analysis we quantify global emissions of modern volatile fluorinated anesthetics over the past 13 years and assess the fates of these compounds in the atmosphere.

During the past decade the fluranes have become the inhalation anesthetics of choice in most developed countries although nitrous oxide (N_2O) and halothane are still applied in human anesthesiology around the world. Halothane was intensively used in the 1960s and 1970s but has been replaced in developed countries due to its potential for liver injuries ("halothane hepatitis") [*Halpern*, 1993]. Methoxyflurane (1960s and 1970s) was the first halogenated ether used in anesthesiology but was also phased out due to medical side effects [*Halpern*, 1993]. Enflurane was used from the 1970s to the 1990s [*Ball and Westhorpe*, 2007a] and was replaced by isoflurane (early 1980s) [*Halpern*, 1993], which is presently still used, in particular in veterinary anesthesia [e.g., *Enz et al.*, 2013]. Desflurane (1992) [*Halpern*, 1993] and sevoflurane (mid-1990s) [*Ball and Westhorpe*, 2007b] are the most recently introduced inhalation anesthetics.

Table 1. Properties and Results for the Anesthetics Halothane, Isoflurane, Desflurane, and Sevoflurane: Greenhouse Warming Potentials (GWPs) Are Based on a 100 Year Time Frame, and Abundances Are Expressed as Dry Air Mole Fractions in Parts Per Trillion (10^{-12})[a]

	Clinical Introduction	Atmospheric Lifetime (Year)	GWP (100 Year)	Radiative Efficiency (mW m^{-2} ppb^{-1})	Abundance[b] (ppt)	Emissions[b] (t yr^{-1})	Radiative Forcing[b] 2014 (mW m^{-2})	Radiative Forcing[b] BAU (mW m^{-2})	Radiative Forcing[b] Growth (mW m^{-2})
Halothane	1956[c,d]	1.0[e]	50[f]	130[g]	0.0092	250	0.0012	0.0011	—
Isoflurane	1981[h]	3.2[i]	510[i]	420[g]	0.097	880	0.041	0.043	0.082
Desflurane	1992[h]	14[j]	2540[j]	450[g]	0.30	960	0.13	0.22	0.35
Sevoflurane	1993–1995[k]	1.1[j]	130[j]	370[g]	0.13	1200	0.047	0.00	0.097

[a] Abundances, emissions, and radiative forcing are global and for 2014. Projections on radiative forcing for the business-as-usual (BAU) and Growth scenarios are detailed in the text and are for 2050.
[b] This work.
[c] *Bovill* [2008].
[d] *Robinson and Toledo* [2012].
[e] *Carpenter et al.* [2014].
[f] *Sulbaek Andersen et al.* [2012a].
[g] *Hodnebrog et al.* [2013].
[h] *Halpern* [1993].
[i] *Sulbaek Andersen et al.* [2010].
[j] *Sulbaek Andersen et al.* [2012b].
[k] *Ball and Westhorpe* [2007b].

In modern human anesthesia these compounds are evaporated into a stream of medical gases (oxygen, N_2O, and medical breathing air). These breathing mixtures are administered to the patient through an airway device (e.g., laryngeal mask or tracheal tube) using an anesthetic machine, which is designed as semiclosed breathing system with an overflow and a return recycling stream that includes carbon dioxide (CO_2) removal. The rates of in vivo metabolization are small, 0.2 %, <0.02 %, and 5 %, for isoflurane, desflurane, and sevoflurane, respectively, and with ≈20% somewhat larger for halothane [*Halpern*, 1993; *Sherman et al.*, 2012]. Because there are currently no mandatory or routine waste anesthetic gas capture systems, virtually all of the anesthetics used escape to the atmosphere. To protect personnel, these drugs are directly vented to the outside through the ventilation systems in modern operating theaters. In contrast to modern operating theaters, there are also anesthetics application in less controlled environments such as, e.g., farm-based veterinary anesthesia [*Enz et al.*, 2013], where usage efficiency of the applied inhalation anesthetics and personnel protection are reduced.

2. Methods

2.1. Measurements

We made atmospheric measurements of halothane (2-bromo-2-chloro-1,1,1-trifluoroethane, $CF_3CHClBr$, halon-2311), isoflurane ((RS)-2-chloro-2-(difluoromethoxy)-1,1,1-trifluoro-ethane, $CF_3CHClOCHF_2$, HCFE-235da2), desflurane (1,2,2,2-tetrafluoroethyl difluoromethyl ether, $CF_3CHFOCHF_2$, HFE-236ea2), and sevoflurane (1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy)propane, $(CF_3)_2CHOCH_2F$, HFE-347 isomer). The measurements were made with a "Medusa" gas chromatograph mass spectrometer using large, 4 L sample volumes [*Miller et al.*, 2008] (see supporting information for analytical details). Flask samples were collected at remote sites in the Northern Hemisphere since 2000, aboard the icebreaker research vessel *Araon* during an expedition in the North Pacific in 2012, and at the South Korea Antarctic station King Sejong (South Shetland Islands, 62.2°S, 58.8°W, *Vollmer et al.* [2011]). While these samples capture hemispheric background conditions, we have also been tracking these anesthetics in air masses that are more directly influenced by anthropogenic releases. For this, we have been conducting 2-hourly in situ ground-based measurements since early 2013 at the high-altitude (3580 m) observatory at Jungfraujoch (Switzerland), with an atmospheric "footprint" (source-receptor relationship) covering large parts of Western Europe. The site is mostly influenced by free tropospheric air, but particularly in summer it is in the atmospheric boundary layer and convection of air masses with regional loading of trace gases reaches the site. Jungfraujoch is also influenced by larger-scale uplifts from the European boundary layer, mainly during the passage of fronts (see *Brunner et al.* [2012] for more details).

Measurements are also ongoing from a rooftop in Dubendorf (suburban Zurich, Switzerland), where we regularly intercept air masses that are strongly influenced by nearby emissions. The mean flask sample measurement precisions (2σ) were 11%, 6.7%, 3.8%, and 16% for halothane, isoflurane, desflurane, and

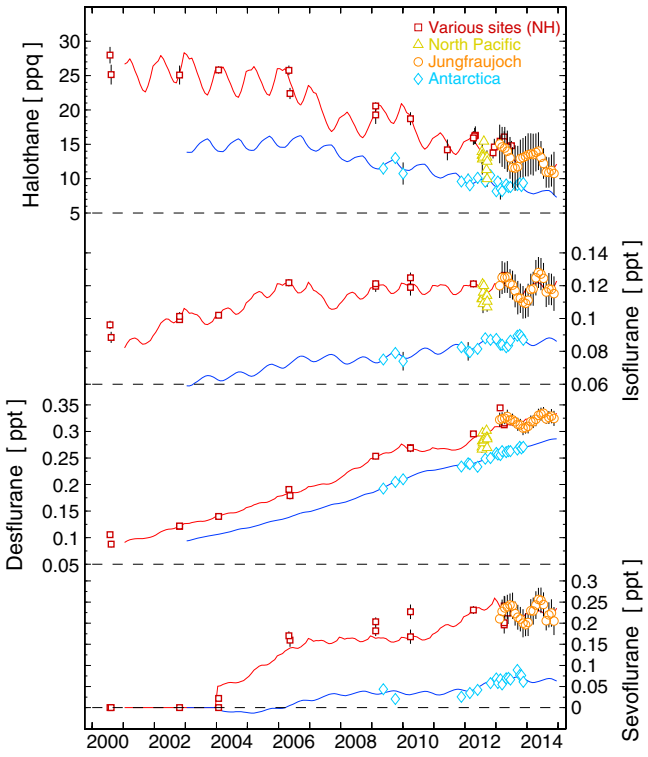

Figure 1. Atmospheric records of halogenated anesthetics: The four anesthetics halothane, isoflurane, desflurane, and sevoflurane in samples collected in the Northern Hemisphere at various locations during clean air conditions, from the North Pacific, from Jungfraujoch, and from the Korean Antarctic Station King Sejong. Vertical bars for the flask samples denote measurement precisions ($\pm 1\sigma$) and, if not seen, are smaller than the symbol size. Jungfraujoch data are monthly means of background-filtered measurements with vertical bars denoting ($\pm 1\sigma$) variability. The solid lines are modeled mole fractions for the model surface boxes 30°N to 90°N (in red) and 30°S to 90°S (in blue).

sevoflurane, respectively. The precisions for the in situ measurements are generally poorer due to the lower sample volumes (2 L) and the simultaneous acquisition of many other compounds. They are approximately (2σ) 40%, 8%, 5%, and 10% for the four compounds, respectively. The results are reported on the Empa-2013 primary calibration scale for these anesthetics. This scale is based on the generation of a ppt-level reference standard with estimated calibration scale uncertainties of 10% for each of the compounds (see detailed description in the supporting information).

2.2. Model

To calculate global emissions from our observations, we used a two-dimensional model of atmospheric transport and chemistry that resolved four latitudinal semihemispheres, with divisions at 30° and at the equator, and three vertical levels with boundaries at 500 hPa and 200 hPa [*Rigby et al.*, 2013]. We combine the observations and the model with inverse methods to quantify emissions. We use a Bayesian methodology in which an a priori estimate of the rate of change of emissions is optimized using the available observations [*Rigby et al.*, 2011, 2014], assuming that the uncertainty on the a priori estimated bottom-up emissions growth rates were accurate to ±50 % per year (see supporting information for more details on the model calculations).

3. Results and Discussions

3.1. Atmospheric Observations

Halothane is present in the atmosphere at ppq (parts per quadrillion, 10^{-15}) dry air mole fractions with declining abundances in both hemispheres, which reached a record low of 8.5 ppq in air over Antarctica during the austral summer 2012/2013 (Figure 1). The abundance is so low, despite multidecadal emissions, mainly because of its relatively short lifetime of ≈1 year [*Carpenter et al.*, 2014]. However, its persistent interhemispheric gradient indicates ongoing emissions with predominantly northern hemispheric origin. At Jungfraujoch and Dubendorf, we did not detect freshly polluted air, confirming the phaseout of halothane within the footprints of these European stations (see Figure S2 in the supporting information).

In contrast, the three fluranes have grown significantly in the atmosphere over the observed time period, with mean background mole fractions at Jungfraujoch in 2014 (January–November) of 0.12 ppt (parts per trillion, 10^{-12}) for isoflurane, 0.32 ppt for desflurane, and 0.23 ppt for sevoflurane. Pronounced lower mole fractions in the remote Antarctic air compared to the Northern Hemisphere suggest predominant northern hemispheric emissions. The North Pacific measurements agree with the northern hemispheric trends observed from the other sampling locations, although there is some interesting variability in the results. Low abundances in a few samples were found to be due to the interception of air that was advected from far south, while comparatively elevated mole fractions were detected in air masses that originated from the Asian continent where they, presumably, intercepted emissions of these anesthetics (see Figure S1). Air that

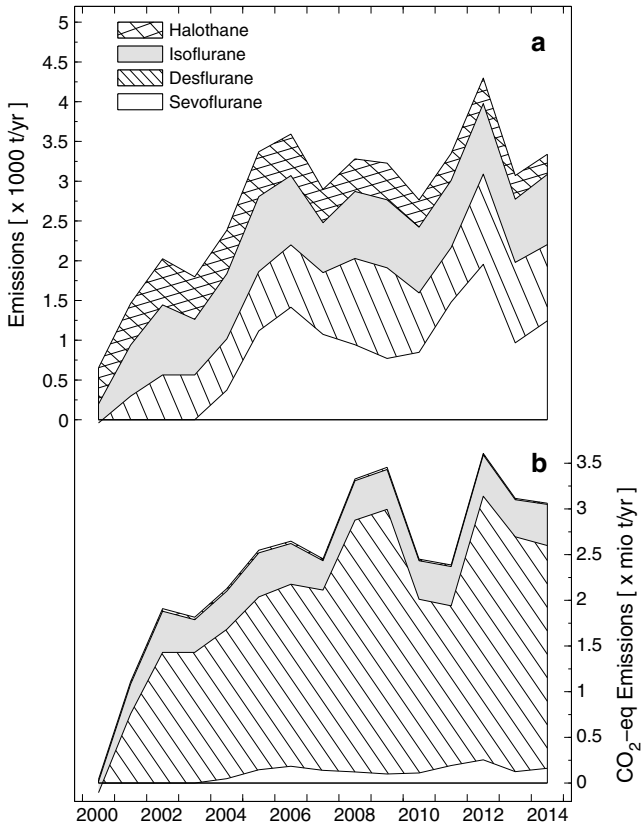

Figure 2. Global emissions of inhalation anesthetics: (a) emissions on a per-ton basis of the anesthetics halothane, isoflurane, desflurane, and sevoflurane and (b) emissions in units of CO_2 equivalents using Global Warming Potentials (GWPs) based on a 100 year time frame.

is loaded with recently emitted fluranes can also be detected at Jungfraujoch and dominates the picture of the urban air at Dubendorf, proving the presence of nearby emissions sources. With these emission events removed from the data, the Jungfraujoch flurane records show pronounced seasonal cycles. These are predominantly caused by the seasonally varying atmospheric abundance of the hydroxyl radical, which is the main reactant in atmospheric flurane destruction.

Using the derived emissions (see below), the model is run in a forward mode to simulate the global atmospheric mole fractions. In general, our model reproduces the measurements within the combined uncertainties in analyses and model (Figure 1). However, for isoflurane and sevoflurane the model underestimates the seasonal cycle at Jungfraujoch, perhaps reflecting uncertainties in our estimates of atmospheric lifetimes for these substances, or possibly because the model uses interannually repeating wind fields and therefore cannot capture potentially anomalous transport events.

3.2. Emissions and Consumptions

For halothane we find declining global emissions, from 490 t yr^{-1} for the 2000/2001 mean to 250 t yr^{-1} in 2014 (Table 1 and Figure 2). In contrast, the flurane emissions increased over the same period, with isoflurane increasing from 440 to 880 t yr^{-1} and desflurane increasing from 150 t yr^{-1} to 960 t yr^{-1}. For sevoflurane, our measurement detection limits are higher than those of the other compounds. As a consequence, the earliest emissions we can quantify are in 2004, where we infer emissions of 1100 t, which rose to 1200 t yr^{-1} in 2014. While all three fluranes are presently released in similar quantities, their CO_2 equivalent emissions are dominated by desflurane, which has the largest Global Warming Potential (GWP) of all anesthetics discussed here (Table 1). We calculate total emissions of 3.1 $\pm$ 0.6 million t CO_2 eq (100 year Global Warming Potential (GWP)) for the four anesthetics in 2014, with ≈80 % stemming from desflurane. These total emissions are equivalent to one third of the CO_2 emissions of the Swiss passenger car fleet for that year [*BAFU*, 2010].

We compared our top-down emissions to available bottom-up estimates. Recent bottom-up studies estimate that ≈4.4 million t CO_2 eq globally (excluding halothane, *Sulbaek Andersen et al.* [2010]) and 5.6 million t CO_2 eq for 2013 in the United States (excluding halothane, including N_2O, *Sherman et al.* [2014]). Uncertainties in both methodologies are large, but also, differences of this relative magnitude between top-down and bottom-up emission estimates are not uncommon for anthropogenic greenhouse gases [see, e.g., *Vollmer et al.*, 2011; *O'Doherty et al.*, 2014]. They demonstrate the need for independent methodologies in the assessment and reporting of emissions [*Nisbet and Weiss*, 2010; *Weiss and Prinn*, 2011].

Using our emissions estimates we can derive global production and usage figures. Assuming no other significant sinks during usage (no scavenging/destruction in the operating theater), the only correction to be applied is for the metabolic rates during anesthetic applications. For halothane we estimate a global 2014 usage of 280 $\pm$ 120 t yr^{-1}, assuming that only half of the administered drug is reaching the patient where

it then undergoes metabolism at the before-mentioned rate of 20%. This usage is still surprisingly high compared to bottom-up estimates of "below 1000 t" in the late 1980s [*Rodgers and Ross*, 1989] and given that this compound has been undergoing phaseout over the past two decades. For the fluranes the production and usage deviate from the emissions insignificantly due to the low metabolic rates.

Among the four anesthetics discussed here, halothane and isoflurane have the potential to destroy stratospheric ozone due to their bromine (halothane only) and chlorine-bearing molecules. However, the contributions of these two compounds to stratospheric ozone loss are very small given their relatively short lifetimes (Table 1) and low Ozone Depletion Potentials (halothane 0.14–0.4 [*Pyle et al.*, 1991; *Sulbaek Andersen et al.*, 2012a] and isoflurane 0.01 [*Sulbaek Andersen et al.*, 2012a]). Neither of the two anesthetics is part of the Montreal Protocol on Substances That Deplete the Ozone Layer, and the halothane phaseout was not triggered by climate concerns. In this respect, the contribution to stratospheric ozone loss by the anesthetic N_2O is likely more significant.

Predictions of the future impact of halothane and the fluranes on the global atmosphere are uncertain, given that, historically, anesthetics have been phased in and out relatively frequently. Nevertheless, we ran some simplified scenarios with our model, to estimate future mole fractions and radiative forcing for the three fluranes. In a business-as-usual (BAU) scenario, we kept the 2014 emissions constant over the next decades, and in a "Growth" scenario we increased them each year by 2% yr^{-1}. The combined radiative forcing for the four anesthetics for 2014 is 0.22 mW m^{-2}. It increases to 0.32 mW m^{-2} under the BAU scenario and to 0.53 mW m^{-2} under the Growth scenario by 2050 (Table 1). By comparison, the radiative forcing due to "F gases" (mainly hydrofluorocarbons and perfluorocarbons) listed in the Kyoto Protocol is currently 33 mW m^{-2} and is estimated to be 30–300 mW m^{-2} in 2050 [*Rigby et al.*, 2014; *Velders et al.*, 2009]. If the Montreal Protocol long-lived halocarbon greenhouse gases (under phaseout) are included, then the radiative forcing of these synthetic greenhouse gases was 350 mW m^{-2} in 2012 and is estimated to be 300–500 mW m^{-2} in 2050 [*Rigby et al.*, 2014; *Velders et al.*, 2009].

4. Conclusions

The contributions of most anthropogenic halocarbons to global warming are relatively small (compared to, e.g., CO_2) when viewed in isolation, and this is also true for the anesthetics discussed here. However, collectively, these gases can have an appreciable influence on radiative forcing [*Rigby et al.*, 2014]. Owing to regulations in place, in particular the "Montreal Protocol" (even though targeted to reduce ozone depletion gases), prevented the halocarbon emissions from reaching significantly larger contributions to the anthropogenically induced radiative forcing [*Velders et al.*, 2012]. Also, the European F-gas Directive No. 842/2006 is targeted at reducing the current F-gas emissions, although fluorinated anesthetics are not included in these regulations.

In this context it is also worth mentioning that N_2O is another inhalation anesthetic presently in use. Its radiative forcing and its contribution to stratospheric ozone depletion due to emissions from anesthesia could not be estimated by our top-down methodology because this compound has significant other sources to the atmosphere than from anesthesia alone.

To assess the impacts of anesthetics on the atmosphere, an integrated view is required. For example, while xenon is the anesthetics with the least direct climate impact, the climate fingerprint of its extraction from air probably outweighs its benefits over the fluranes. Similarly, recycling and scavenging from the exhaust of the airway device are measures that need to be carefully addressed, not only in terms of human safety and health but also for their environmental cost benefits [*Sherman et al.*, 2012; *McCulloch*, 2001]. Reduced consumption [*Feldman*, 2012] and switching to intravenous anesthetics are measures that are likely to reduce the impact on the atmosphere. When choosing between the fluranes it is evident that desflurane is the largest contributor to the radiative forcing. While some of its medical properties appear desirable (e.g., fast emergence due to low blood solubility), the large quantities that must be used for each surgery, due to its high Minimum Alveolar Concentration of ≈6 vol % (compared to, e.g., ≈2 vol % for sevoflurane [*Halpern*, 1993]) along with its atmospheric properties, make it an undesirable compound from the climate perspective.

Acknowledgments
This research was conducted under the auspices of the European FP7 Infrastructure Project "Integrated Non-CO_2 Greenhouse gas Observing System" (InGOS). Financial support was also provided through the project HALCLIM by the Swiss Federal Office for the Environment (FOEN), by the Swiss State Secretariat for Education and Research and Innovation (SERI) and by the National Research Foundation of Korea for the Korean-Swiss Science and Technology Cooperation Program. Further support comes from the International Foundation High Altitude Research Stations Jungfraujoch and Gornergrat (HFSJG), and the European Metrology Research Programme ENV52 project Metrology for high-impact greenhouse gases" (HIGHGAS). We acknowledge the personnel at the Jungfraujoch observatory and at the King Sejong station, and the crew of the R/V *Araon* for instrumental and logistical support. We also acknowledge the many providers of flask samples composing the archived air record. Continuous support from colleagues in the Advanced Global Atmospheric Gases Experiment (AGAGE) is acknowledged. M. R. is supported by an advanced research fellowship from the UK Natural Environment Research Council (NERC) NE/1021365/1. T. S. R. acknowledges financial support from the Korean Polar Research Program PE13410. Keyhong Park helped to calculate backward trajectories for the SHIPPO-2012 results.

The Editor thanks Jodi Sherman and an anonymous reviewer for their assistance in evaluating this paper.

References

BAFU, Bundesamt fuer Umwelt (2010), *Luftschadstoff-Emissionen des Strassenverkehrs 1990–2035. Aktualisierung 2010*, p. 130, Bundesamt für Umwelt, Bern.

Ball, C., and R. N. Westhorpe (2007a), Enflurane, *Anesth. Intensive Care*, *35*(3), 325.

Ball, C., and R. N. Westhorpe (2007b), Sevoflurane, *Anesth. Intensive Care*, *35*(6), 835.

Bovill, J. G. (2008), Inhalation anaesthesia: From diethyl ether to xenon, in *Modern Anesthetics. Handbook of Experimental Pharmacology*, vol. 182, edited by J. Schüttler and H. Schwilden, pp. 121–142, Springer, Berlin.

Brunner, D., S. Henne, C. A. Keller, S. Reimann, M. K. Vollmer, S. O'Doherty, and M. Maione (2012), An extended Kalman-filter for regional scale inverse emission estimation, *Atmos. Chem. Phys.*, *12*, 3455–3478, doi:10.5194/acp-12-3455-2012.

Carpenter, L. J., S. Reimann, J. B. Burkholder, C. Clerbaux, B. D. Hall, R. Hossaini, J. C. Laube, and S. A. Yvon-Lewis (2014), Ozone-Depleting Substances (ODSs) and other gases of interest to the Montreal protocol, chapter 1, in *Scientific Assessment of Ozone Depletion: 2014, Global Ozone Research and Monitoring Project—Rep. 55*, World Meteorol. Organ., Geneva, Switzerland.

Enz, A., G. Schüpbach-Regula, R. Bettschart, E. Fuschini, E. Bürgi, and X. Sidler (2013), Erfahrungen zur Schmerzausschaltung bei der Ferkelkastration in der Schweiz Teil 1: Inhalationsanästhesie, *Schweiz. Arch. Tierh.*, *155*(12), 651–659, doi:10.1024/0036-7281/a000530.

Feldman, J. M. (2012), Managing fresh gas flow to reduce environmental contamination, *Anesth. Analg.*, *114*(5), 1093–1101, doi:10.1213/ANE.0b013e31824eee0d.

Halpern, D. F. (1993), Recent developments in fluorine substituted volatile anesthetics, in *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, 48th ed., edited by R. Filler, Y. Kobayashi, and L. M. Yagupolskii, pp. 101–133, Studies in Organic Chemistry, Elsevier, Amsterdam, Netherlands.

Hodnebrog, Ø., M. Etminan, J. S. Fuglestvedt, G. Marston, G. Myhre, C. J. Nielsen, K. P. Shine, and T. J. Wallington (2013), Global warming potentials and radiative efficiencies of halocarbons and related compounds: A comprehensive review, *Rev. Geophys.*, *51*, 300–378, doi:10.1002/rog.20013.

Ishizawa, Y. (2011), General anesthetic gases and the global environment, *Anesth. Analg.*, *112*(1), 213–217, doi:10.1213/ANE.0b013e3181fe02c2.

Langbein, T., H. Sonntag, D. Trapp, A. Hoffmann, W. Malms, E.-P. Röth, V. Mörs, and R. Zellner (1999), Volatile anaesthetics and the atmosphere: Atmospheric lifetimes and atmospheric effects of halothane, enflurane, isoflurane, desflurane and sevoflurane, *Br. J. Anaesth.*, *82*(1), 66–73.

McCulloch, A. (2000), Correspondence to: Volatile anaesthetics and the atmosphere: Atmospheric lifetimes and atmospheric effects of halothane, enflurane, isoflurane, desflurane and sevoflurane, *Br. J. Anaesth.*, *84*(4), 534–536.

McCulloch, A. (2001), Correspondence to: Volatile anaesthetics and the atmosphere: An end to 'scavenging'?, *Br. J. Anaesth.*, *86*(4), 596.

Miller, B. R., R. F. Weiss, P. K. Salameh, T. Tanhua, B. R. Greally, J. Mühle, and P. G. Simmonds (2008), Medusa : A sample preconcentration and GC/MS detector system for in situ measurements of atmospheric trace halocarbons, hydrocarbons, and sulfur compounds, *Anal. Chem.*, *80*(5), 1536–1545, doi:10.1021/ac702084k.

Mychaskiw, G., II, and E. I. Eger II (2013), A different perspective on anesthetics and climate change, *Anesth. Analg.*, *116*(3), 734–735, doi:10.1213/ANE.0b013e318280dfd0.

Nisbet, E., and R. Weiss (2010), Top-down versus bottom-up, *Science*, *328*, 1241–1243, doi:10.1126/science.1189936.

O'Doherty, S., et al. (2014), Global emissions of HFC-143a (CH_3CF_3) and HFC-32 (CH_2F_2) from in situ and air archive atmospheric observations, *Atmos. Chem. Phys.*, *14*, 9249–9258, doi:10.5194/acp-14-9249-2014.

Pyle, J. A., D. Wuebbles, S. Solomon, and S. Zvenigorodsky (1991), Ozone depletion and chlorine loading potentials, chapter 6, in *Scientific Assessment of Ozone Depletion: 1991, Global Ozone Research and Monitoring Project—Rep. 25*, World Meteorol. Organ., Geneva, Switzerland.

Rigby, M., A. L. Ganesan, and R. G. Prinn (2011), Deriving emissions from sparse mole-fraction time series, *J. Geophys. Res.*, *116*, D08306, doi:10.1029/2010JD015401.

Rigby, M., et al. (2013), Re-evaluation of lifetimes of the major CFCs and CH_3CCl_3 using atmospheric trends, *Atmos. Chem. Phys.*, *13*, 2691–2702, doi:10.5194/acp-13-2691-2013.

Rigby, M., et al. (2014), Recent and future trends in synthetic greenhouse gas radiative forcing, *Geophys. Res. Lett.*, *41*, 2623–2630, doi:10.1002/2013GL059099.

Robinson, D. H., and A. H. Toledo (2012), Historical development of modern anesthesia, *J. Invest. Surg.*, *25*, 141–149, doi:10.3109/08941939.2012.690328.

Rodgers, R. C., and J. A. S. Ross (1989), Anaesthetic agents and the ozone layer, *Lancet*, 1209–2010.

Ryan, S. M., and C. J. Nielsen (2010), Global warming potential of inhaled anesthetics: Application to clinical use, *Anesth. Analg.*, *111*(1), 92–98, doi:10.1213/ANE.0b013e3181e058d7.

Sherman, J. (2013), Response to: A different perspective on anesthetics and climate change, *Anesth. Analg.*, *116*(3), 734–735, doi:10.1213/ANE.0b013e318280dff4.

Sherman, J., C. Le, V. Lamers, and M. Eckelman (2012), Life cycle greenhouse gas emissions of anesthetic drugs, *Anesth. Analg.*, *114*(5), 1086–1090, doi:10.1213/ANE.0b013e31824f6940.

Sherman, J. D., R. B. Schonberger, and M. Eckelman (2014), Estimate of carbon dioxide equivalents of inhaled anesthetics in the United States, in *Proceedings of the American Society of Anesthesiologists Annual Meeting*, New Orleans, La., 11–15 Oct.

Sulbaek Andersen, M. P., S. P. Sander, O. J. Nielsen, D. S. Wagner, T. J. Sanford Jr., and T. J. Wallington (2010), Inhalation anaesthetics and climate change, *Br. J. Anaesth.*, *105*(6), 760–766, doi:10.1093/bja/aeq259.

Sulbaek Andersen, M. P., O. J. Nielsen, T. J. Wallington, B. Karpichev, and S. P. Sander (2012a), Assessing the impact on global climate from general anesthetic gases, *Anesth. Analg.*, *114*(5), 1081–1085, doi:10.1213/ANE.0b013e31824d6150.

Sulbaek Andersen, M. P., O. J. Nielsen, B. Karpichev, T. J. Wallington, and S. P. Sander (2012b), Atmospheric chemistry of isoflurane, desflurane, and sevoflurane: Kinetics and mechanisms of reaction with chlorine atoms and OH radicals and global warming potentials, *J. Phys. Chem.*, *116*, 5806–5820, doi:10.1021/jp2077598.

Velders, G. J. M., D. W. Fahey, J. S. Daniel, M. McFarland, and S. O. Andersen (2009), The large contribution of projected HFC emissions to future climate forcing, *Proc. Natl. Acad. Sci. U.S.A.*, *106*(27), 10,949–10,954, doi:10.1073/pnas.0902817106.

Velders, G. J. M., A. R. Ravishankara, M. K. Miller, M. J. Molina, J. Alcamo, J. S. Daniel, D. W. Fahey, S. A. Montzka, and S. Reimann (2012), Preserving Montreal Protocol climate benefits by limiting HFCs, *Science*, *335*, 922–923, doi:10.1126/science.1216414.

Vollmer, M. K., et al. (2011), Atmospheric histories and global emissions of the anthropogenic hydrofluorocarbons HFC-365mfc, HFC-245fa, HFC-227ea, and HFC-236fa, *J. Geophys. Res.*, *116*, D08304, doi:10.1029/2010JD015309.

Weiss, R. F., and R. G. Prinn (2011), Quantifying greenhouse-gas emissions from atmospheric measurements: A critical reality check for climate legislation, *Philos. Trans. R. Soc. London, Ser. A*, *369*, 1925–1942, doi:10.1098/rsta.2011.0006.