DEPARTMENT OF ANESTHESIOLOGY

JOURNAL CLUB

Thursday March 9, 2017
1800 HOURS

LOCATION:
Aqua Terra Restaurant
1 Johnson Street

PRESENTING ARTICLES:
Dr. Christopher Haley & Sarah Maxwell

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SUGGESTED GUIDELINES FOR CRITICAL APPRAISAL OF PAPERS
ANESTHESIOLOGY JOURNAL CLUB
QUEEN'S UNIVERSITY

Two presenters will be assigned to choose and present summaries of their papers. Ideally the two papers will represent similar topics but contrasting research methodologies. The focus remains on critical appraisal of the research and manuscript, more than on the actual contents of the article. Each presenter will then lead an open discussion about the article, based around the guidelines below. The object is to open up the appraisal to wide discussion involving all participants, who will be expected to contribute pending suspension of bar privileges.

GENERAL

1. Title of paper: Does it seem like an important problem? Does it reflect the purpose/results?
2. Authors, institution and country of origin

INTRODUCTION

1. What is the problem being addressed?
2. What is the current state of knowledge of the problem studied?
3. What is the hypothesis being tested?
4. How does testing the hypothesis help solve the stated problem?

METHODOLOGY

1. Study design:
    a) Clinical trial vs. systematic review/meta-analysis
    b) Prospective vs. retrospective
    c) Observational vs. Experimental
    d) Randomized or not
    e) Blinded or not

2. Population studied:
    a) Human, animal, other
    b) Justification
    c) Control groups: experimental vs. historical
    d) Is the sample size/power calculated, and how?
    e) Is the population similar to your own practice?
    f) Single vs. multi-centre

3. Is the study ethically sound?
    a) Clinical equipoise
    b) Does treatment meet standard of care (esp controls)?
    c) Appropriate consent and institutional ethics approval

4. Exclusions: what groups are excluded and why?

5. Experimental protocol
    a) Is it designed to test the hypothesis?

b) Is it detailed enough to be reproducible?
c) Is the methodology validated?
d) Are the drugs/equipment used detailed?
e) How does the randomization take place?

6. What are the primary endpoints?
7. Is power sufficient to justify secondary endpoints?
8. Is the protocol clinically relevant?
9. Data collection and analysis
10. Statistical analysis: Is it appropriate? Are results

RESULTS

1. Are the groups comparable?
2. Were any subjects/data eliminated?
3. Analyzed by intent to treat?
4. Are adequate details of results provided? - data, graphs, tables

DISCUSSION

1. What is the main conclusion of the study?
2. Do the results support this conclusion?
3. Do the results address the stated purpose/hypothesis of the study?
4. How do the authors explain the results obtained?
5. Are there any alternative interpretations to the data?
6. Are the results clinically as well statistically relevant?
7. How do the results compare with those of previous studies?
8. What do the results add to the existing literature?
9. What are the limitations of the methods or analysis used?
10. What are the unanswered questions for future work?

APPLICABILITY OF THE PAPER

1. Have you learned something important from reading this paper?
2. Will the results of this study alter your clinical practice?
3. Was the food and wine up to the high standards expected by self-respecting anesthesiologists?

British Journal of Anaesthesia **105** (6): 760–6 (2010)
Advance Access publication 8 October 2010 · doi:10.1093/bja/aeq259

BJA

CLINICAL PRACTICE

Inhalation anaesthetics and climate change†

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Key points

- The important role of CO_2 in contributing to climate change is well known, but the contribution of volatile anaesthetic agents is not well established.
- The estimated contributions of isoflurane, sevoflurane, and desflurane were calculated.
- Yearly emissions of anaesthetic agents are estimated to be equivalent to the CO_2 emissions from of 1 million cars or one coal-fired power plant.
- Presently, the impact of volatile anaesthetics is small but nevertheless important to consider. The choice of anaesthetic should be clinically based.

Background. Although the increasing abundance of CO_2 in our atmosphere is the main driver of the observed climate change, it is the cumulative effect of all forcing agents that dictate the direction and magnitude of the change, and many smaller contributors are also at play. Isoflurane, desflurane, and sevoflurane are widely used inhalation anaesthetics. Emissions of these compounds contribute to radiative forcing of climate change. To quantitatively assess the impact of the anaesthetics on the forcing of climate, detailed information on their properties of heat (infrared, IR) absorption and atmospheric lifetimes are required.

Methods. We have measured the IR spectra of these anaesthetics and conducted calculations of their contribution to radiative forcing of climate change recognizing the important fact that radiative forcing is strongly dependent on the wavelength of the absorption features.

Results. Radiative efficiencies of 0.453, 0.469, and 0.351 W m^{-2} ppb^{-1} and global warming potentials (GWPs) of 510, 1620, and 210 (100 yr time horizon) were established for isoflurane, desflurane, and sevoflurane, respectively.

Conclusions. On the basis of the derived 100 yr GWPs, the average climate impact per anaesthetic procedure at the University of Michigan is the same as the emission of ~22 kg CO_2. We estimate that the global emissions of inhalation anaesthetics have a climate impact which is comparable with that from the CO_2 emissions from one coal-fired power plant or 1 million passenger cars.

Keywords: global warming potential; greenhouse gas; infrared absorption; radiative forcing; spectra

Accepted for publication: 9 August 2010

Human activities result in the release of a large quantity and variety of chemical compounds into the atmosphere. These compounds undergo atmospheric transport and transformation and impact the environment and human health on different spatial and temporal scales. The past decade has seen increased interest in human-induced climate change with impacts on society and human health.[1] A substantial effort has been dedicated to assessing the direct and indirect impacts of human activities on climate. In such assessments, it is important to consider all activities. We address here the potential impact of the commonly used anaesthetic agents isoflurane, desflurane, and sevoflurane.

Global climate change is caused primarily by the increased atmospheric concentrations of the major long-lived greenhouse gases CO_2, CH_4, N_2O, and halogenated organic compounds. Radiative forcing is a measure of the magnitude, and thus importance, of a particular driver of climate change in altering the balance of incoming and outgoing energy in the Earth's energy budget. The change in the atmospheric concentration of CO_2 as a result of human activities (mainly fossil fuel combustion, but also deforestation), from ~275 ppm prior to the industrial revolution to ~390 ppm today, contributes +1.7 W m^{-2} to radiative forcing of climate change.[2] Halogenated organic compounds are an important category of greenhouse gases. Although present at an atmospheric concentration approximately a million times lower than CO_2, halogenated organic compounds are responsible for a combined warming effect of ~0.3 W m^{-2}.[2]

† This article is accompanied by the Editorial.

The efficacy of halogenated organic compounds arises primarily because they absorb strongly in the infrared (IR) region of the electromagnetic spectrum, which overlaps the peak at ~8–14 μm (700–1300 cm^{-1}) in the spectrum of the outgoing terrestrial IR radiation known as the 'atmospheric window' (Fig. 1). Emission of IR radiation through the 'atmospheric window' into space is an important mechanism by which the Earth cools itself (as seen from Fig. 1, emission at wavelengths outside the 'window' is also important). The addition of molecules to the atmosphere which hinder the escape of IR radiation through the 'atmospheric window' has a powerful effect on climate.

Isoflurane (HCFE-235da2, $CF_3CHClOCHF_2$), desflurane ($CF_3CHFOCHF_2$), and sevoflurane [$(CF_3)_2CHOCH_2F$] are halogenated organic compounds used for induction and maintenance of general anaesthesia. Isoflurane entered broad clinical use in the early 1980s, followed by desflurane and sevoflurane a decade later. The volatile anaesthetic gases are delivered via a system that mixes the anaesthetic gas with a carrier gas (oxygen and nitrous oxide) in various concentrations. Exhaled gases flow through an absorber, most commonly calcium hydroxide, which is used to remove carbon dioxide. Some gas may at the same time escape from the delivery system. The flow rate by which the gas is delivered in terms of litre min^{-1} represents the rate at which fresh gas flows into the re-breathing system and can have a significant impact on the amount of gas released into the environment. These flow rates vary both within, and among, institutions, based on practice and surgical procedure. For example, at the University of Michigan, a typical, large US hospital, annual usage (2009) of the gases is 1081, 6, and 505 litre of isoflurane, desflurane, and sevoflurane, respectively (quoted volumes are for the liquids). A small fraction (3–5%) of sevoflurane is taken up and metabolized, while isoflurane and desflurane are one and two orders of magnitude less vulnerable to metabolism, respectively.[3] Thus, the vast majority of these anaesthetics will be released to the environment in the course of their use.

Previous assessments of the impact of the atmospheric release of these anaesthetics have not accounted for the well-established fact that absorptions at different frequencies have markedly different contributions to forcing (Fig. 1). Consequently, the existing information concerning the climatic impact of these important and widely used anaesthetics is

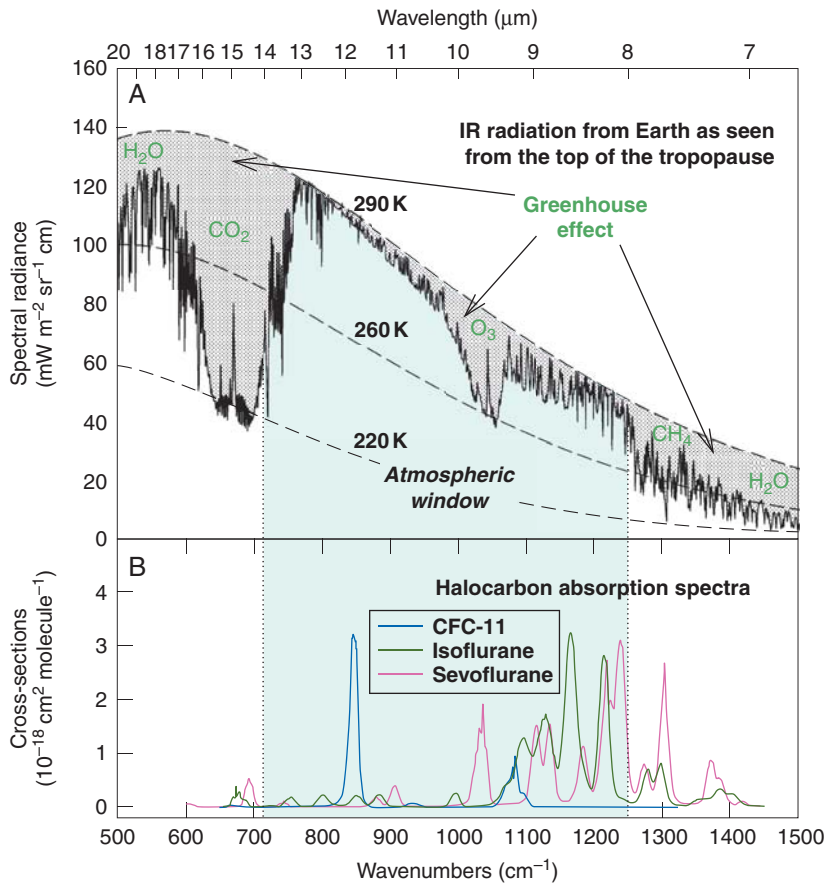

Fig 1 (A) The net upward atmospheric radiance spectrum at the tropopause.[22] Dashed lines are Planck functions for blackbody emissions at 290, 260, and 220 K, respectively. (B) IR absorption bands for CFC-11 (CCl_3F), isoflurane, and sevoflurane. Halogenated organic compounds absorb strongly in 'the atmospheric window' region.

rather uncertain. To provide a more precise accounting of the environmental impact of these compounds, we have measured the IR spectra of isoflurane, desflurane, and sevoflurane and evaluated their radiative properties. We present here substantially revised and, we believe, the first accurate assessment of the climate impact of these species.

Methods

The change in net radiation at the tropopause caused by a given change in greenhouse gas concentration in the atmosphere is referred to as radiative efficiency, F_x. Radiative efficiency has units of W m^{-2} ppb^{-1} and depends upon the strength and spectral position of the absorption bands of a compound. Integrating the radiative efficiency over time gives the Absolute Global Warming Potential (AGWP) for time horizon t' defined as:[4]

$$\mathrm{AGWP}_x(t') = \int_0^{t'} F_x[x(t)]\,\mathrm{d}t \qquad (1)$$

where F_x is the radiative forcing per unit mass of species x, $x(t)$ describes the decay with time of a unit pulse of compound x, and t' is the time horizon considered. The AGWP has units of W m^{-2} ppb^{-1} yr and quantifies the future integrated radiative forcing to the time horizon of a unit mass pulse emission of a greenhouse gas. The global warming potential (GWP) metric was developed to compare the integrated effect of various compounds on climate. It is by no means the only metric which can be used for comparing future climate impacts of emissions of greenhouse gases. However, it is a metric adopted in national and international agreements (e.g. UNFCCC Kyoto Protocol)[2] and we choose to use it here as well. The GWP for time horizon t' can be defined as:[4]

$$\mathrm{GWP}_x(100) = \frac{\int_0^{t'} F_x \exp(-t/\tau_x)\,\mathrm{d}t}{\int_0^{t'} F_{\mathrm{CO}_2} R(t)\,\mathrm{d}t} \qquad (2)$$

where F_{CO_2} is the radiative forcing of CO_2, $R(t)$ the response function that describes the decay of an instantaneous pulse of CO_2, and the decay of the pulse of compound x has been rewritten assuming that it obeys a simple exponential decay curve determined by a response time of τ_x. The denominator in expression (2) is the AGWP for CO_2 which has been evaluated by the WMO and IPCC as 0.676 W m^{-2} ppm^{-1} [2 4] for a 100 yr time horizon. Expression (2) can then be rewritten as:

$$\mathrm{GWP}_x(100) = \frac{\int_0^{t'} F_x \exp(-t/\tau_x)\,\mathrm{d}t}{0.676} \qquad (3)$$

Although our understanding of the atmospheric chemistry of isoflurane is reasonably mature,[5] the atmospheric fate and radiative properties of desflurane and sevoflurane are not well defined. Furthermore, the GWPs for all three compounds have only been coarsely estimated based on normalizing the integrated IR absorption cross-sections relative to that of CFC-12.[6 7] Among other things, this approach does not take into account that the Planck function, describing the atmosphere's radiative transfer over the spectral region in which halogenated organic compounds absorb, is not an ideal blackbody curve, but diverges dramatically due to the spectral overlaps of other radiatively active species. Herein we use a method, outlined by Pinnock and colleagues,[8] in which the measured absorption cross-sections of the anaesthetics are weighted by an instantaneous cloudy-sky radiative forcing calculated for a model atmosphere with global mean specification of cloudiness and accounting for absorption by CO_2, O_3, and water vapour.

Results

The IR spectra of isoflurane, desflurane, and sevoflurane were recorded with a spectral resolution of 0.25 cm^{-1} using a Mattson Sirus 100 FTIR spectrometer interfaced to a 140 litre Pyrex gas cell with an analytical path length of 27.1 m. Calibrated spectra over the spectral range 650–2000 cm^{-1} are shown in Figure 2, and integrated absorption cross-sections are tabulated in Table 1, together with previous literature values. As shown in the insets in Figure 2, the absorbance scaled linearly with anaesthetic partial pressure. We estimate our IR absorption cross-sections to be accurate within 5%. Using the IR spectra shown in Figure 2, we calculate radiative efficiencies of 0.453, 0.469, and 0.351 W m^{-2} ppb^{-1} for isoflurane, desflurane, and sevoflurane (Table 2). The method outlined above assumes that the anaesthetics are well mixed in the atmosphere. As discussed elsewhere,[9] compounds with short atmospheric lifetimes will not be completely well mixed in the atmosphere, and as a result, the radiative efficiencies derived might be overestimated by up to 20%.

The atmospheric lifetimes for isoflurane, desflurane, and sevoflurane are determined by their reactivity towards hydroxyl (OH) radicals. The atmospheric lifetimes are the reciprocals of the pseudo first-order rate constants (k') for their removal:

$$\text{Atmospheric lifetime}\,(\tau) = \left(\frac{1}{k'}\right) \qquad (4)$$

Experimentally determined bimolecular rate constants for the reaction of OH radicals with the anaesthetics need to be converted into pseudo first-order rate constants k'. This is achieved by multiplying the bimolecular rate constants by the atmospheric OH concentration ([OH]). A global weighted-average OH concentration of 1.0×10^6 molecule cm^{-3} is used in our calculations.[10]

The rates of reactions of OH radicals with isoflurane, desflurane, and sevoflurane have been reported at room temperature (298 K).[6 7 11 12] However, the appropriate temperature to use for the atmospheric lifetime calculation is 272 K.[13] The temperature dependence of rate coefficients is described by the Arrhenius expression as $k = A\times\exp(E_a/RT)$ cm^3 $molecule^{-1}$ s^{-1} for the temperature T. The pre-exponential Arrhenius parameter A and the activation energy E_a can be estimated from the measured rate coefficient at 298 K.[14] Using this approach, we derive values of $k(\mathrm{OH}+\text{isoflurane}) = 1.01\times10^{-14}$, k(OH+desflurane)

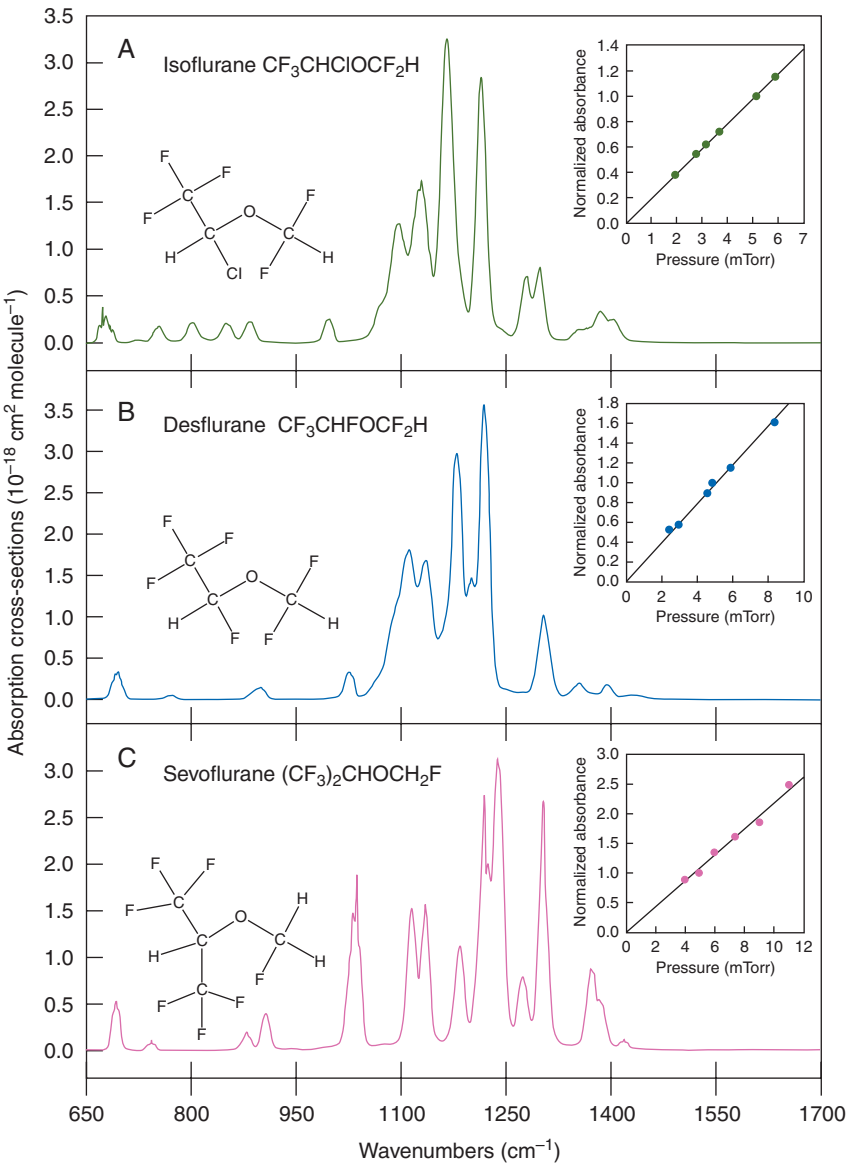

Fig 2 IR absorption spectra of the common anaesthetics, isoflurane (A), desflurane (B), and sevoflurane (C). Insets show the linearity of IR absorption as a function of pressure.

$=3.55\times10^{-15}$, and k(OH+sevoflurane)$=1.79\times10^{-14}$ cm^3 molecule^{-1} s^{-1} at 272 K. Combining these rate coefficients with the global weighted-average OH concentration of 1.0×10^6 molecule cm^{-3} [10] leads to estimated atmospheric lifetimes of 3.2, 8.9, and 1.8 yr for isoflurane, desflurane, and sevoflurane, respectively. Uncertainties associated with the estimated lifetimes are dominated by uncertainty in the OH rate constants (probably $\pm$20%).

Substituting the radiative efficiency and atmospheric lifetime values into expression (3) gives GWPs for isoflurane, desflurane, and sevoflurane of 510, 1620, and 210, respectively. Table 1 compares our calculated radiative efficiency, atmospheric lifetimes, and GWPs with the existing literature values. As seen from Table 1, the GWPs determined in the present work are very similar to those reported by Langbein and colleagues[7]. However, on close inspection, this agreement is fortuitous as it reflects cancelling errors. For example, Langbein and colleagues use what we believe to be an inappropriately long lifetime for desflurane (21.4 yr).

Discussion

There are no production numbers available in the literature for the anaesthetic agents. The three compounds have not yet been observed in the free atmosphere, and current atmospheric levels are expected to be small (of the order of part per trillion/volume). At these concentrations, when viewed in isolation, their present contribution to the relative

forcing of climate change is negligible in comparison with the current forcing of 1.7 W m^{-2} due to CO_2 (reflecting an increase from the preindustrial level of 270–280 to the current level of ~390 ppm/volume).[15] It should be emphasized, however, that the cumulative impact of many smaller contributors, for example, CFCs and other halogenated organic compounds, do combine to become significant in the overall magnitude of the forcing of climate change.

In the absence of data on current atmospheric concentration levels for the anaesthetics, the usefulness of GWP, as a forward-looking time-integrated impact measure of a pulse emission of 1 kg of a gas, relative to CO_2, becomes particularly evident. To put the results above into perspective, we can estimate the climate impact of emissions of anaesthetics from a typical large-size hospital, based on the 100 yr GWP values determined in this work. Using the quantities and mix of anaesthetic agents used annually at the University of Michigan (see above), we calculate a climate impact equivalent to the emission of 1000 t of CO_2. About 46 000 anaesthetic procedures are performed annually at the University of Michigan, thus the agent mix-averaged impact per procedure is equal to ~22 kg CO_2-eq (carbon dioxide equivalents).

Table 1 Integrated absorption cross-sections for isoflurane, desflurane, and sevoflurane at 298 K. †Empirical estimate based on analogy to other anaesthetics

Compound	Integrated absorption cross-sections (cm molecule^{-1})		
	Brown and colleagues[6] (800–1200 cm^{-1})	This work (800–1200 cm^{-1})	This work (650–1500 cm^{-1})
Isoflurane $CF_3CHClOCHF_2$	1.6×10^{-16}	1.86×10^{-16}	2.91×10^{-16}
Desflurane $CF_3CHFOCHF_2$	1.2×10^{-16}†	1.94×10^{-16}	3.13×10^{-16}
Sevoflurane $(CF_3)_2CHOCH_2F$	0.90×10^{-16}	1.15×10^{-16}	3.02×10^{-16}

Although no publicly available data exist on the total number of anaesthetic procedures that are performed annually in the USA, it is generally assumed to be in the order of 30 million. We estimate that the total US emissions of inhaled anaesthetics have a climate impact equivalent to the yearly emissions of 660 000 t of CO_2. Weiser and colleagues[16] recently estimated the number of major surgical procedures undertaken yearly worldwide as 187–281 million, with major surgical procedures defined as requiring local or general anaesthesia or sedation. Of this worldwide number of procedures, 73.6% were provided in middle- and high-income countries, where the usage of inhaled anaesthetics to induce and maintain general anaesthesia is common practice. Hence, it seems reasonable to assume that ~200 million anaesthetic procedures are performed worldwide on an annual basis. Proceeding on this assumption, we estimate that the annual climate impact, as measured by the 100 yr GWP, of global emissions of inhaled anaesthetics, is equivalent to that from the emission of ~4.4 million t of CO_2. The average coal-fired power plant in the USA emits 3.85 million t of CO_2 per year[17] while a typical passenger car in the USA emits 5.03 t of CO_2 per year.[18] Hence, we conclude that global emissions of inhalation anaesthetics, when measured by the 100 yr GWP, have a contribution to the radiative forcing of climate change which is comparable with that of the CO_2 emissions from one coal-fired power plant or approximately 1 million passenger cars.

Nitrous oxide, which is analgesic, but to some extent also amnestic, has a GWP of 298 on a 100 yr time horizon[2] and is often used in amounts up to 60% of the carrier gas. It should be noted that co-administration of nitrous oxide during the anaesthetic procedure will increase the overall impact of anaesthetic procedure on climate.

While our paper was in review, the results from a similar study were published by Ryan and Nielsen.[19] The integrated IR absorption cross-sections of isoflurane, desflurane, and sevoflurane [2.85 (0.03), 3.03 (0.07), and 3.06 (0.06)$\times10^{-16}$ cm molecule^{-1}, respectively] and the radiative efficiencies (0.453, 0.447, and 0.365 W m^{-2}) reported by Ryan and Nielsen are indistinguishable from the results obtained in our study. Ryan and Nielsen reported GWPs for 20, 100, and

Table 2 Summary of radiative properties, atmospheric lifetimes, and GWP for isoflurane, desflurane, and sevoflurane. *Assuming an average global concentration of OH radicals of 1×10^6 molecules cm^{-3}.[10] †Using an integration time horizon of 100 yr. ‡Using $k(OH+CF_3CHClOCHF_2, 272\ K)=1.01\times10^{-14}$, derived from Arrhenius expression in Tokuhashi and colleagues.[11] ¶Converted from HGWP values (relative to CFC-12), using GWP (CFC-12)=10 890.[4] §Using $k(OH+CF_3CHFOCHF_2, 272\ K)=3.55\times10^{-15}$ cm^3 molecule^{-1} s^{-1}, based on the unweighted average of values from Langbein and colleagues[7] and Oyaro and colleagues[12] (5.7×10^{-15} cm^3 molecule^{-1} s^{-1}, 298 K), and adjusted for temperature dependence according to DeMore.[14] ||Using $k[OH+(CF_3)_2CHOCH_2F, 272\ K]=1.79\times10^{-14}$ cm^3 molecule^{-1} s^{-1}, based on Langbein and colleagues[7] (2.7×10^{-14} cm^3 molecule^{-1} s^{-1}, 298 K) and adjusted for temperature dependence according to DeMore[14]

Compound	Atmospheric lifetime* (yr)	Radiative efficiencies (W m^{-2} ppb^{-1})	Global warming potentials†			
			This work	Brown and colleagues[6]	Langbein and colleagues[7]	WMO[4]
Isoflurane $CF_3CHClOCHF_2$	3.2‡	0.453	**510**	328¶	545¶	349
Desflurane $CF_3CHFOCHF_2$	8.9§	0.469	**1620**	–	1525¶	—
Sevoflurane $(CF_3)_2CHOCH_2F$	1.8||	0.351	**210**	54¶	218¶	—

500 yr time horizons in the supporting information of their paper. Ryan and Nielsen give 100 yr time horizon GWPs of 429, 1314, and 106 for isoflurane, desflurane, and sevoflurane, respectively. These values (especially for sevoflurane) differ from our findings. To understand the origin of this difference, we attempted to reproduce the GWP values reported by Ryan and Nielsen using the method and data described in their paper. Unfortunately, we could not reproduce their results. The GWP values calculated in Ryan and Nielsen are in error.[20] Using radiative efficiencies and lifetime values from Ryan and Nielsen, CFC-11 data from Forster and colleagues,[2] and the method of Ryan and Nielsen (note there is a typo in the HGWP expression on page 5 of the supporting information from Ryan and Nielsen; the ratio of molecular weights should be reversed) we recalculate 100 yr GWPs of 571, 1746, and 141 for isoflurane, desflurane, and sevoflurane, respectively. The results for isoflurane and desflurane are indistinguishable, within the experimental uncertainties, from our values. The result for sevoflurane is ~30% lower than our value and reflects the fact that Ryan and Nielsen estimated the atmospheric lifetime of sevoflurane using data from Brown and colleagues[6] and Langbein and colleagues.[7] As discussed by Calvert and colleagues,[21] there are systematic errors in the work of Brown and colleagues which lead to an underestimation of atmospheric lifetimes. We believe that the 1.8 yr atmospheric lifetime of sevoflurane estimated in the present work based on the work by Langbein and colleagues[7] is more reliable than that used by Ryan and Nielsen, and hence our GWP estimate for sevoflurane should be preferred.

In this report, we present a new set of measurements to evaluate the climate impact of three inhaled anaesthetic agents widely used by the medical community. The data provided here significantly improve our understanding of the atmospheric chemistry and the radiative properties for these compounds, on which basis the climatic impact of activities that involve the use, and release to the atmosphere, of halogenated anaesthetic agents can be evaluated more accurately.

Acknowledgements

This work was performed partly at the Jet Propulsion Laboratory, California Institute of Technology, under a contract with the National Aeronautics and Space Administration. We thank David Wallington for a careful reading of the manuscript.

Conflict of interest

None declared.

Funding

O.J.N. acknowledges financial support from the Danish Natural Science Research Council, EUROCHAMP2, and the Villum Kann Rasmussen Foundation for the Copenhagen Center for Atmospheric Research (CCAR). M.P.S.A. is supported by an appointment to the NASA Postdoctoral Program, administered by Oak Ridge Associated Universities through a contract with NASA.

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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
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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

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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

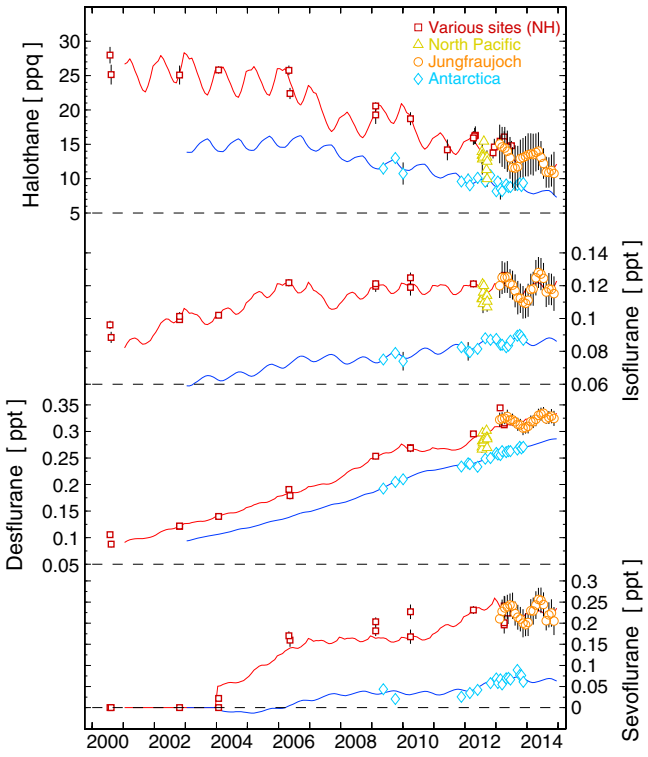

Figure 1. Atmospheric records of halogenated anesthetics: The four anesthetics halothane, isoflurane, desflurane, and sevoflurane in samples collected in the Northern Hemisphere at various locations during clean air conditions, from the North Pacific, from Jungfraujoch, and from the Korean Antarctic 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

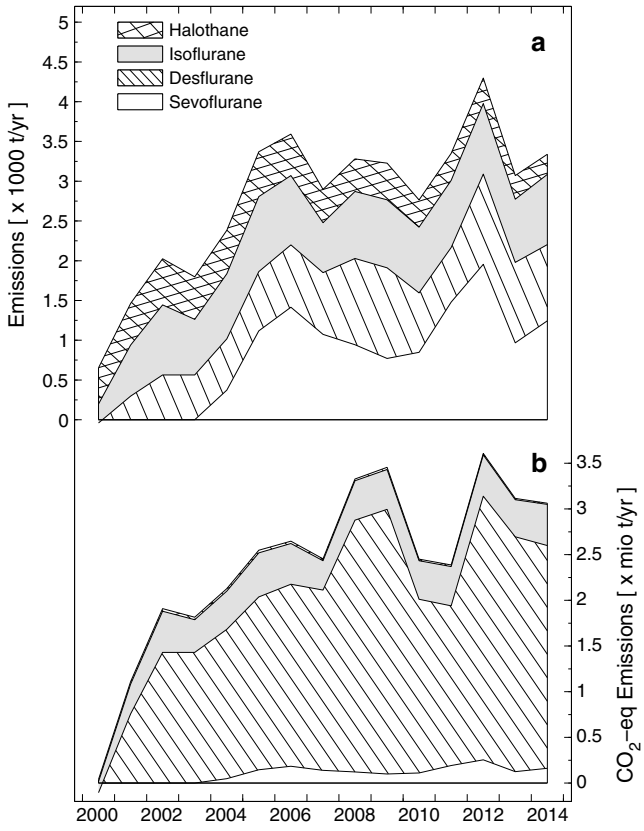

Figure 2. Global emissions of inhalation anesthetics: (a) emissions on a per-ton basis of the anesthetics halothane, isoflurane, desflurane, and sevoflurane and (b) emissions in units of CO_2 equivalents using Global Warming Potentials (GWPs) based on a 100 year time frame.

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.

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