Review Article / บทฟื้นฟูวิชาการ

The Perfluorocarbon Paradox: Historical Legacy and Residual Use of Isoflurane and Enflurane in Anesthesia Practice

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Abstract

This review article critically examines the paradoxical persistence of isoflurane and enflurane in anesthesia practice, despite well-documented concerns about their perfluorocarbon (PFC) composition and environmental impact. While these agents historically offered advantages in rapid induction, ease of administration, and cost-effectiveness, their continued use must now be weighed against newer, more environmentally sustainable alternatives such as sevoflurane and desflurane. Recent regulatory frameworks and updated studies emphasize the need to reduce volatile anesthetic emissions, as PFCs contribute significantly to global warming potential. Clinical considerations including enflurane's association with epileptiform EEG activity have contributed to its withdrawal from most markets. By integrating historical perspectives, updated comparative pharmacology, and regulatory and environmental considerations, this article highlights multifaceted challenges and risk mitigation strategies, including engineering controls, administrative policies, and sustainable practice guidelines.

Keywords: anesthesia practice, desflurane, enflurane, isoflurane, perfluorocarbon, sevoflurane

Introduction

Isoflurane and enflurane are volatile halogenated ethers that played transformative roles in anesthesia practice during the latter half of the 20th century. Their favorable pharmacokinetic profiles including rapid onset and offset, manageable cardiovascular effects, and straightforward administration, contributed to their widespread adoption at the time, largely supplanting older, less stable agents like ether and chloroform. However, these agents are composed of perfluorocarbons (PFCs), which chemically stable and effective as anesthetics, are potent greenhouse gases with long atmospheric lifespans. Historically,

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Received March 15, 2024, Revised June 14, 2025, Accepted June 14, 2025

PFCs were even investigated for their ability to facilitate oxygen and carbon dioxide transport, but environmental concerns about their persistence and bioaccumulation have become increasingly significant.

Isoflurane remains in limited use today, primarily in veterinary practice and resource-limited settings. Enflurane has been largely discontinued in human medicine due to its tendency to provoke epileptiform EEG activity and its unfavorable side-effect profile. Recent regulatory updates, including the EU F-Gas Regulation[1] and the WHO Environmental Report[2], emphasize transitioning toward low-emission anesthetic agents like sevoflurane and desflurane. These newer agents offer faster induction and emergence times and align better with sustainability goals, although they come with trade-offs in terms of cost and environmental impact.[3] This review examines the historical role of isoflurane and enflurane, their pharmacological properties, comparative performance with newer agents, and the regulatory frameworks that shape their continued use or phase-out.

Isoflurane, introduced in the 1970s, quickly gained popularity due to its favorable pharmacokinetic profile and low solubility in blood, allowing for rapid induction and recovery from anesthesia.[4] Enflurane, introduced earlier in the 1960s, also saw widespread use for its similar properties, although it was later overshadowed by isoflurane due to concerns about hepatotoxicity. These agents played a pivotal role in shaping contemporary anesthesia practice by facilitating safer and more efficient anesthesia induction and maintenance, reducing the incidence of perioperative complications, and improving patient outcomes. Their continued use in anesthesia practice underscores their enduring legacy and ongoing relevance in the field of perioperative medicine.

Chemical structures and properties

Isoflurane and enflurane are both halogenated ethers that belong to the class of volatile anesthetic agents. They are composed of carbon, hydrogen, and fluorine atoms, with the distinguishing feature being their PFC composition. PFCs are characterized by the presence of carbon-fluorine bonds, which impart exceptional stability and resistance to chemical and biological degradation. In the case of isoflurane and enflurane, the substitution of hydrogen atoms with fluorine atoms results in the formation of perfluorinated compounds, contributing to their unique properties as volatile anesthetic agents.[5]

Pharmacokinetics and pharmaco-dynamics

Isoflurane and enflurane share similar pharmacokinetic profiles characterized by inhalational administration, rapid uptake due to high lipid solubility, and minimal systemic metabolism (0.2% for isoflurane; up to 2% for enflurane).[6] The bulk of the anesthetic is exhaled unchanged, which historically minimized concerns about systemic toxicity but raises modern concerns about occupational exposure and greenhouse gas emissions.[3] Both agents potentiate GABA A receptor activity and

suppress excitatory neurotransmission, producing reversible CNS depression and immobility.[7] However, enflurane's unique proconvulsant effect at higher concentrations or in hypoventilated states remains clinically relevant; it may induce epileptiform EEG patterns, especially during light planes of anesthesia.[8] This contrasts with isoflurane, which is generally considered to have more stable electrophysiologic effects, though both agents require careful titration in patients with seizure predisposition.[7]

Clinical limitations

Enflurane is well-documented to induce epileptiform EEG changes, particularly during hypocapnia and hyperventilation.[9] These seizure-like discharges posed risks during anesthesia maintenance and limited its desirability for neuroanesthesia and obstetric contexts.[10] This adverse profile, combined with the emergence of safer alternatives, led to its gradual withdrawal from human clinical markets by the early 1990s in most regions. Isoflurane tends to produce predictable EEG suppression without the same proconvulsant risk, making it preferable in patients with epilepsy or when precise depth-of-anesthesia monitoring is required.[11] Despite these pressures, isoflurane and enflurane remain in use in many low- and middle-income countries due to cost advantages and supply chain constraints. Therefore, the conversation must remain pragmatic: balancing patient safety, practitioner health, and environmental stewardship with the realities of diverse healthcare settings.[3]

Comparison with modern agents

Modern depth-of-anesthesia monitors, such as bispectral index (BIS) and processed EEG algorithms, have become essential tools for tailoring agent concentrations and minimizing awareness while optimizing emergence. These technologies reinforce the need for individualized agent selection and highlight opportunities to integrate legacy agents into safer, and more sustainable practice.[9] Advancements in anesthetic pharmacology have led to a gradual shift from older halogenated agents like isoflurane and enflurane to newer volatile anesthetics such as sevoflurane and desflurane. Both sevoflurane and desflurane offer faster induction and emergence due to their lower blood–gas partition coefficients, which can enhance perioperative efficiency and reduce recovery times.[7] This trade-off has led to nuanced guidelines that encourage selective use based on patient needs, facility ventilation, and carbon footprint considerations. Such environmental considerations have prompted guidelines that advocate judicious agent selection, balancing patient-specific needs with institutional sustainability goals.

Understanding perfluorocarbons

PFCs are a group of synthetic chemicals composed of carbon and fluorine atoms. They are known for their unique properties, including high stability, resistance to heat, chemicals, biological degradation and electricity, as well as low surface tension. These properties make

them useful in a variety of industrial and consumer applications.[12] PFCs have excellent thermal stability and are used as coolants and heat transfer fluids, such as electronics manufacturing and semiconductor production, due to their insulating properties. PFCs are used as solvents, lubricants, and additives, including the production of textiles, and coatings. Some PFCs are used in fire extinguishing systems due to their inertness and ability to displace oxygen, which helps to suppress fires. Furthermore, they are used in the manufacturing of fluoropolymers, which are used in non-stick coatings (e.g., Teflon), lubricants, and sealants.[13]

PFCs may still be used in some specialized medical applications, such as liquid ventilation for neonatal respiratory distress syndrome. They can also be used as blood substitutes due to their ability to carry and deliver oxygen.[14] A significant concern associated with the use of isoflurane and enflurane is their environmental impact, particularly with regards to PFC emissions. While these compounds are chemically inert and generally considered safe for short-term anesthesia use, prolonged or repeated exposure may pose health risks to patients and healthcare workers.[15] Inhalation of waste anesthetic gases containing PFCs may lead to respiratory irritation, liver toxicity, exacerbation of pre-existing lung conditions, renal impairment, and reproductive effects.[16]

Exposure to PFCs in daily life[17]

PFCs can contaminate water sources through industrial discharge, landfill leachate, and firefighting foam runoff. They can accumulate in the environment and food chain, particularly in seafood and other products with high fat content. Some consumer products, such as non-stick cookware, waterproof clothing, and stain-resistant fabrics, may contain PFCs. These chemicals can leach from the products and be absorbed through skin contact or inhalation of fumes. PFCs used in products like carpet treatments and furniture coatings can release into indoor air over time, leading to inhalation exposure.

Teflon Cookware and DuPont's role in PFOA concerns

DowDuPont, formed through a merger with Dow Chemical Company, is among the world's largest chemical corporations. Historically, as DuPont, it played a significant role in perfluorinated compound production. Its connection with perfluorooctanoic acid (PFOA) stems from Teflon manufacturing. Teflon, a brand name for polytetrafluoroethylene (PTFE), is widely used as a non-stick coating for cookware, including pots and pans, owing to its non-stick properties simplifying cooking and cleaning processes. However, DuPont faced legal and regulatory scrutiny over its handling of PFOA and its potential adverse health and environmental impacts.[18] In 2005, DuPont settled with the Environmental Protection Agency (EPA), agreeing to pay fines for failing to disclose information about PFOA's health risks. Concerns have been raised about Teflon pan safety due to potential perfluorinated compound release at high temperatures, emitting fumes containing toxic gases like PFOA and perfluorooctane

sulfonate (PFOS).[18] While primary health risks come from overheating and prolonged exposure to fumes, some studies suggest even regular use at typical cooking temperatures may lead to low-level perfluorinated compound exposure. In response, many manufacturers phased out PFOA use in Teflon and other non-stick coatings.[19]

Potential risks associated with duration of exposure

Despite PFCs' beneficial properties, the environmental persistence and potential toxicity of PFCs have raised concerns about their impact on human health and the environment. The acute and chronic toxicity of PFCs can vary depending on factors such as the specific chemical structure of the compound, the dose, duration of exposure, and route of exposure inhalation, ingestion, or skin contact.[20] Acute exposure to high concentrations of certain PFCs is relatively rare. It can cause adverse health effects, including respiratory irritation, headache, nausea, dizziness, and in severe cases, pulmonary edema and central nervous system depression.[20] Chronic exposure to PFCs has raised concerns due to their potential to accumulate in the body over time. Some PFCs, such as PFOA and PFOS, have been associated with various adverse health effects in animal studies and epidemiological studies, including adverse effects on cardiorespiratory, hepatic, renal, and endocrine systems, developmental, immune system, and carcinogenicity.[20] PFCs are potent greenhouse gases and persistent organic pollutants with a high global warming potential. They can accumulate in the environment and contribute to climate change, air and water pollution when released into the atmosphere.

Strategies for mitigating risks

Engineering controls, such as efficient scavenging systems and ventilation systems, can help minimize exposure to waste anesthetic gases containing PFCs. These systems capture and remove exhaled anesthetic gases from the operating room environment. Administrative controls, such as workplace policies and procedures, can help mitigate risks associated with PFC exposure. This may include limiting the duration and frequency of exposure, providing adequate training and education for healthcare workers, and enforcing proper handling and disposal practices for volatile anesthetic agents. Ensuring that healthcare workers have access to appropriate PPE, such as respiratory protection and gloves, can help minimize direct contact and inhalation of PFCs during anesthesia administration and waste gas scavenging. PPE should be worn consistently and in accordance with established safety protocols to reduce the risk of occupational exposure.[21]

Environmental stewardship and sustainability in anesthesia practice is crucial for minimizing the environmental impact of PFCs. Healthcare facilities can promote sustainability by implementing initiatives to reduce waste, conserve resources, and adopt eco-friendly alternatives to volatile anesthetic agents. This may involve using reusable anesthesia

equipment, optimizing delivery systems, and advocating for environmentally responsible practices. Sustainable anesthesia practices, such as efficient scavenging systems to capture waste gases and minimize emissions, are vital for reducing the environmental footprint of volatile anesthetic agents and fostering environmental stewardship in healthcare settings.[22]

Regulations and restrictions

Efforts to phase out or reduce the use of PFCs in consumer products, industrial processes, and medical applications continue to evolve worldwide. Many companies have voluntarily committed to eliminating or minimizing PFCs in their products. Completely removing PFCs from daily life remains challenging due to their widespread use and environmental persistence. However, individuals can still reduce their exposure by selecting PFC-free products, avoiding contaminated water and food sources, and supporting policies aimed at minimizing PFC emissions and environmental contamination.

Various regulations and international agreements govern the use and release of PFCs, especially compounds like PFOA and PFOS, which are known for their adverse health and environmental effects. In the United States, the EPA has established lifetime health advisories for PFOA and PFOS in drinking water and has facilitated the phase-out of PFOS production under its PFOA Stewardship Program.[23] Similarly, the European Chemicals Agency[24], restricts the use of PFOA and related substances.[22] At the global level, PFCs fall under the Stockholm Convention on Persistent Organic Pollutants, which seeks to eliminate or restrict the production and use of chemicals that persist in the environment.[24]

In the field of anesthesia, volatile anesthetic agents are regulated to ensure patient safety and limit environmental impact. Before approval for clinical use, these agents undergo rigorous safety and efficacy testing, overseen by regulatory bodies such as the U.S. Food and Drug Administration[25] and the European Medicines Agency.[26] Guidelines from professional organizations like the American Society of Anesthesiologists[5] and the European Society of Anaesthesiology[27] provide recommendations on proper dosing, administration, monitoring, and waste gas management. Healthcare facilities are required to implement scavenging systems to capture waste anesthetic gases, monitor emissions, and report adverse events to regulatory authorities.

From an environmental perspective, the greenhouse gas impact of volatile anesthetics has received heightened attention. Updated regulations, such as the European Union's F-Gas Regulation[1,25] and international frameworks like the Montreal Protocol[28], now encourage healthcare providers to adopt lower-emission agents and advanced scavenging or destruction technologies. Many hospitals are also implementing engineering controls, closed-circuit anesthesia, and alternative techniques like TIVA to reduce reliance on volatile agents with high global warming potential.

Future directions and considerations

As anesthesia continues to evolve, the residual use of legacy agents like isoflurane and enflurane highlights the importance of embracing innovation while addressing lingering challenges. Emerging alternatives such as newer low-global-warming-potential inhalational agents, advanced intravenous anesthetic protocols, and closed-circuit or low-flow anesthesia delivery systems, offer promising avenues to reduce greenhouse gas emissions without compromising perioperative care. Moreover, advancements in engineering controls, such as more effective gas scavenging and destruction technologies, can further mitigate occupational exposure and environmental release. At an institutional level, integrating environmental impact assessments into anesthesia practice guidelines, education, and procurement decisions will be vital. Professional societies and regulatory bodies must continue to advocate for policies that incentivize sustainable practices and ensure that low-resource settings have equitable access to safer and greener options.

Conclusion

The legacy of isoflurane and enflurane in modern anesthesia practice reflects the specialty's remarkable progress in enhancing patient safety, improving surgical outcomes. The perfluorocarbon paradox reminds us that the benefits of these agents must now be weighed against their residual risks. Anesthesia providers can make informed choices that prioritize both clinical excellence and environmental responsibility. Emerging technologies, alternative anesthetic agents, and robust sustainability strategies will help guide the transition towards a more resilient, future-ready practice.

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