

RESEARCH MONOGRAPH . COMPOUND PROFILE

Halothane

The first clinically successful non-flammable halogenated volatile anesthetic, dominant from 1956 through the 1980s, displaced by ether-class agents owing to halothane hepatitis.

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ABSTRACT

Halothane (2-bromo-2-chloro-1,1,1-trifluoroethane; CAS 151-67-7; molecular formula $C_2HBrClF_3$; molecular weight 197.38) is a halogenated alkane volatile anesthetic synthesized by Charles Suckling at ICI in 1951 and introduced clinically by Michael Johnstone in 1956. Halothane was the first non-flammable volatile to displace diethyl ether and chloroform as the dominant inhalational agent and remained in widespread use through the 1980s before isoflurane and the newer ethers superseded it. The minimum alveolar concentration (MAC) at age 40 is 0.75 percent in oxygen; the blood-gas partition coefficient is 2.4, slower than the modern ether agents. Mechanism is the standard volatile profile (GABA-A potentiation, K2P channel activation, glycine and NMDA modulation). Cardiovascular effects include dose-dependent myocardial depression with preserved or modestly reduced systemic vascular resistance, sensitization to catecholamine-induced arrhythmias (a clinically important interaction with epinephrine), and bradyarrhythmia. The principal limitations that drove displacement are halothane hepatitis (immune-mediated hepatic necrosis with an incidence of approximately 1 in 35,000 cases, attributed to trifluoroacetyl protein adducts generated by 20 percent hepatic metabolism through CYP2E1), and the negative inotropic and arrhythmogenic profile relative to the ether agents. Halothane remains the dominant inhalational anesthetic in lower-resource settings owing to acquisition cost (manufacturer-stated cost approximately one-third of isoflurane). Veterinary use persists in some jurisdictions. The global warming potential is moderate (GWP100 approximately 50). Pediatric induction was a historical strength

owing to the non-pungent character; sevoflurane has displaced halothane for this indication in most jurisdictions.

1. Compound Identification

Halothane is described as halogenated alkane volatile general anesthetic. The first clinically successful non-flammable halogenated volatile anesthetic, dominant from 1956 through the 1980s, displaced by ether-class agents owing to halothane hepatitis.

1.1 Class summary

Halogenated alkane volatile general anesthetic

1.2 Subtitle

The first clinically successful non-flammable halogenated volatile anesthetic, dominant from 1956 through the 1980s, displaced by ether-class agents owing to halothane hepatitis.

2. Abstract

Halothane (2-bromo-2-chloro-1,1,1-trifluoroethane; CAS 151-67-7; molecular formula $\text{C}_2\text{HBrClF}_3$; molecular weight 197.38) is a halogenated alkane volatile anesthetic synthesized by Charles Suckling at ICI in 1951 and introduced clinically by Michael Johnstone in 1956. Halothane was the first non-flammable volatile to displace diethyl ether and chloroform as the dominant inhalational agent and remained in widespread use through the 1980s before isoflurane and the newer ethers superseded it. The minimum alveolar concentration (MAC) at age 40 is 0.75 percent in oxygen; the blood-gas partition coefficient is 2.4, slower than the modern ether agents. Mechanism is the standard volatile profile (GABA-A potentiation, K_2P channel activation, glycine and NMDA modulation). Cardiovascular effects include dose-dependent myocardial depression with preserved or modestly reduced systemic vascular resistance, sensitization to catecholamine-induced arrhythmias (a clinically important interaction with epinephrine), and bradyarrhythmia. The principal limitations that drove displacement are halothane hepatitis (immune-mediated hepatic necrosis with an incidence of approximately 1 in 35,000 cases, attributed to trifluoroacetyl protein adducts generated by 20 percent hepatic metabolism through CYP2E1), and the negative inotropic and arrhythmogenic profile relative to the ether agents. Halothane remains the dominant inhalational anesthetic in lower-resource settings owing to acquisition cost (manufacturer-stated cost approximately one-third of isoflurane). Veterinary use persists in some jurisdictions. The global warming potential is moderate (GWP100 approximately 50). Pediatric induction was a historical strength owing to the non-pungent character; sevoflurane has displaced halothane for this indication in most jurisdictions.

3. Mechanism of Action

Standard volatile profile: GABA-A potentiation, K2P channel activation, glycine and NMDA modulation. Distinguished by myocardial depression, catecholamine sensitization, and 20 percent hepatic metabolism producing immunogenic trifluoroacetyl adducts.

The mechanistic profile described above represents the consensus position from peer-reviewed literature where available; for compounds with sparse formal characterization, this section reflects vendor-grade reports and structurally-related class pharmacology and should be interpreted with appropriate caution.

4. Pharmacokinetics and Routes of Administration

Pharmacokinetic data are summarized within the abstract for compounds with formal Phase 1 records. Compounds without published human pharmacokinetic studies are noted as such; investigators should treat the absence of data as a research limitation.

5. Reported Research Dose Ranges

MAC 0.75 percent in oxygen at age 40; clinical maintenance 0.5 to 1.5 percent end-tidal.

Doses are scaled from clinical use where the compound is approved as a medicine, from Phase 2/3 trials where development advanced, or from rodent dose-response data scaled by allometric assumptions where the compound has no human clinical record. Investigators should treat dose ranges from research-chemical-grade vendors as starting points for their own pharmacokinetic and tolerability characterization rather than validated dosing recommendations.

6. Sourcing and Quality Verification

Investigators should obtain analytical confirmation of identity (mass spectrometry; for peptides, additionally amino acid analysis or N-terminal sequencing) and purity (HPLC area-percent, ideally greater than 95 percent) on every lot. Vendor certificates of analysis vary in quality; third-party analytical confirmation through independent laboratories (e.g., Janoshik Analytical, Anabolic Lab) is the gold standard for research-grade peptides and small molecules.

For compounds with established pharmaceutical-grade marketing in any jurisdiction, sourcing from the marketed product (where legal and accessible) provides the highest quality assurance.

7. Reconstitution and Handling

Peptides should be reconstituted in bacteriostatic water or sterile water for injection in the volume appropriate to the desired concentration; lyophilized peptides should be allowed to come to room temperature before reconstitution to minimize precipitation. Reconstituted peptides should be stored refrigerated and used within the timeframe specified by the manufacturer (typically 14 to 30 days for bacteriostatic water reconstitutions, shorter for sterile water).

Small molecules: storage conditions vary by compound; consult the certificate of analysis for the specific product. Most are stable at room temperature in dry, dark conditions; oxidation-sensitive compounds (e.g., catecholamine precursors) require cool storage and protection from light.

8. Stack Interaction Considerations

Investigators combining this compound with other research substances should consider receptor-level interactions (additive effects at shared targets), enzyme-level interactions (CYP-mediated drug-drug interactions where applicable), and pharmacodynamic interactions (additive sedation, additive serotonergic activity, additive hemodynamic effects).

The stack interaction section in published monographs of well-characterized compounds is necessarily incomplete for any specific combination; investigators should treat novel combinations with elevated caution and titrate gradually.

9. References

1. Raventos J. The action of fluothane: a new volatile anaesthetic. Br J Pharmacol Chemother 1956.
2. Brown BR Jr, Gandolfi AJ. Adverse effects of volatile anaesthetics. Br J Anaesth 1987.
3. Kenna JG, Jones RM. The organ toxicity of inhaled anesthetics. Anesth Analg 1995.

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