

RESEARCH MONOGRAPH . COMPOUND PROFILE

# Methoxyflurane

*An early halogenated ether withdrawn for nephrotoxicity but reintroduced in low-dose hand-held inhaler format (Penthrox) for procedural analgesia.*

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## ABSTRACT

Methoxyflurane (2,2-dichloro-1,1-difluoroethyl methyl ether; CAS 76-38-0; molecular formula  $C_3H_4Cl_2F_2O$ ; molecular weight 164.97) is a halogenated methyl ethyl ether developed by Ross Terrell in the 1950s and introduced clinically by Abbott in 1962 (Penthrane). The agent was widely used as a general anesthetic through the early 1970s before reports of dose-dependent nephrotoxicity led to withdrawal as a primary anesthetic in 1974 in the United States. The mechanism of methoxyflurane nephrotoxicity is intrarenal defluorination by CYP2E1 producing inorganic fluoride at concentrations sufficient to inhibit ascending limb chloride transport (high-output renal failure with vasopressin-resistant polyuria, the classical methoxyflurane nephropathy). The threshold for clinically apparent renal injury is approximately 50 micromolar plasma fluoride and is exceeded by general anesthetic doses (MAC 0.16 percent for many hours) but not by the brief, low-dose inhaler format reintroduced as Pentrox in Australia and re-approved in the EU and UK in 2018 for procedural analgesia. The Pentrox formulation delivers approximately 3 mL methoxyflurane through a hand-held disposable inhaler (the green whistle), producing analgesia for procedural pain (extremity injuries, dressing changes, fracture reduction) at exposure levels orders of magnitude below the historical nephrotoxic threshold. The blood-gas partition coefficient is 13, the highest in the class, corresponding to slow induction and prolonged emergence; the clinical Pentrox dose is sub-anesthetic and produces only analgesia and mild sedation. Mechanism includes the standard halogenated ether profile plus

pronounced TRPA1 modulation contributing to the analgesic phenotype.

# 1. Compound Identification

**Methoxyflurane** is described as halogenated ether volatile general anesthetic and analgesic. An early halogenated ether withdrawn for nephrotoxicity but reintroduced in low-dose hand-held inhaler format (Penthrox) for procedural analgesia.

## 1.1 Class summary

Halogenated ether volatile general anesthetic and analgesic

## 1.2 Subtitle

An early halogenated ether withdrawn for nephrotoxicity but reintroduced in low-dose hand-held inhaler format (Penthrox) for procedural analgesia.

## 2. Abstract

Methoxyflurane (2,2-dichloro-1,1-difluoroethyl methyl ether; CAS 76-38-0; molecular formula  $C_3H_4Cl_2F_2O$ ; molecular weight 164.97) is a halogenated methyl ethyl ether developed by Ross Terrell in the 1950s and introduced clinically by Abbott in 1962 (Penthrane). The agent was widely used as a general anesthetic through the early 1970s before reports of dose-dependent nephrotoxicity led to withdrawal as a primary anesthetic in 1974 in the United States. The mechanism of methoxyflurane nephrotoxicity is intrarenal defluorination by CYP2E1 producing inorganic fluoride at concentrations sufficient to inhibit ascending limb chloride transport (high-output renal failure with vasopressin-resistant polyuria, the classical methoxyflurane nephropathy). The threshold for clinically apparent renal injury is approximately 50 micromolar plasma fluoride and is exceeded by general anesthetic doses (MAC 0.16 percent for many hours) but not by the brief, low-dose inhaler format reintroduced as Pentrox in Australia and re-approved in the EU and UK in 2018 for procedural analgesia. The Pentrox formulation delivers approximately 3 mL methoxyflurane through a hand-held disposable inhaler (the green whistle), producing analgesia for procedural pain (extremity injuries, dressing changes, fracture reduction) at exposure levels orders of magnitude below the historical nephrotoxic threshold. The blood-gas partition coefficient is 13, the highest in the class, corresponding to slow induction and prolonged emergence; the clinical Pentrox dose is sub-anesthetic and produces only analgesia and mild sedation. Mechanism includes the standard halogenated ether profile plus pronounced TRPA1 modulation contributing to the analgesic phenotype.

### 3. Mechanism of Action

Standard volatile profile plus TRPA1 modulation contributing to analgesia. Defluorination produces high plasma fluoride at general-anesthetic doses driving the historical nephrotoxicity.

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

Penthrox 3 mL inhaler for procedural analgesia (approximately 6 mL maximum per 24 hours). Historical anesthesia MAC 0.16 percent.

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. Mazze RI, et al. Methoxyflurane nephrotoxicity: a study of dose response in man. JAMA 1971.
2. Cousins MJ, Mazze RI. Methoxyflurane nephrotoxicity. JAMA 1973.
3. Porter KM, et al. Methoxyflurane (Penthrox) for analgesia in trauma: a systematic review. Emerg Med J 2018.
4. Dayan AD. Analgesic use of inhaled methoxyflurane. Hum Exp Toxicol 2016.

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