APPLICATION FOR INCLUSION OF METHOXYFLURANE IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES

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MEDICAL DEVELOPMENTS INTERNATIONAL LIMITED

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1. SUMMARY STATEMENT OF THE PROPOSAL FOR INCLUSION, CHANGE OR DELETION

Methoxyflurane (administered via the Penthrox™ Inhaler) is proposed for the inclusion in the WHO Model List of Essential Medicines for the provision of analgesia and effective management of pain relief.

2. NAME OF THE FOCAL POINT IN WHO SUBMITTING OR SUPPORTING THE APPLICATION

Not applicable (as per e-mail correspondence with Dr. Robin Gray – dated 18th October 2004)

3. NAME OF THE ORGANISATION(S) CONSULTED AND/OR SUPPORTING THE APPLICATION

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4. INTERNATIONAL NONPROPRIETARY NAME (INN, GENERIC NAME) OF THE MEDICINE

Methoxyflurane

5. WHETHER LISTING IS REQUESTED AS AN INDIVIDUAL MEDICINE OR AS AN EXAMPLE OF A THERAPEUTIC GROUP

Listing of Methoxyflurane is requested in two locations in the WHO Model List of Essential Medicines:

1. As an example of a “Pre-operative medication and sedation for short-term procedures” – Section 1.3

2. As a therapeutic group within the “Analgesics, antipyretics, non-steroidal anti-inflammatory medicines (NSAIDs), medicines used to treat gout and disease modifying agents in rheumatoid disorders (DMARDs)” – Section 2

The suggested title for this new therapeutic group is “Non-opioid analgesics”
6. INFORMATION SUPPORTING THE PUBLIC HEALTH RELEVANCE

Pain is defined as “suffering or distress, an unpleasant sensation occurring in varying degrees of severity as a consequence of injury, disease or emotional disorder”. The incidences of pain are worldwide, occur on a daily basis, and present within patients irrespective of nationality, demographic or other identifying factors. It would be difficult to accurately and objectively quantify the incidences of pain throughout the world. The sources of pain are wide and varied, some of which include:

- Physical trauma
- Accidents (i.e., transport, leisure, etc.)
- Injuries (i.e., domestic, industrial, etc.)
- Labour
- Natural disasters (i.e., earthquakes, floods, landslides)
- Mass emergencies
- Man-made inflictions (i.e., war, terrorism, etc.)

The provision of pain relief (analgesia) is of paramount importance in the first stages of patient care. In fact, it is commonly accepted that analgesia should be administered to people inflicted with pain shortly after the A-B-C protocol has been confirmed (Airway – Breathing – Circulation).

With increasing international expectations regarding the humane treatment and effective management of all people inflicted with pain, the increasing incidences of global events that require the effective provision of analgesia (such as mass casualty and disaster situations), and the continued evolution of improved funding and distribution mechanisms to resource-limited nations, the addition of Methoxyflurane to the WHO Model List of Essential Medicines is vital.

7. TREATMENT DETAILS

7.1 Recommended dosage

Methoxyflurane is most effectively supplied in a combination blister pack with either one or two 3 mL sealed bottles of Methoxyflurane and one Penthrox™ Inhaler. The initial priming dose is 3 mL, with a further 3 mL (as required) to prolong the analgesic effect. The amount of Methoxyflurane recommended is based on a maximum 6 mL per day and 15 mL per week per patient.

Methoxyflurane can be administered to children and adults of all ages.

7.2 Duration

3 mL of Methoxyflurane provides approximately 25 – 30 minutes of effective analgesia. An additional 3 mL of Methoxyflurane (total of 6 mL) provides approximately 55 – 60 minutes of effective analgesia.
7.3 Special requirements

Methoxyflurane is to be self-administered under observation (and assisted if necessary) by a person trained in its administration using the hand-held Penthrox™ Inhaler. In essence, the administration of Methoxyflurane is simple and convenient, and there are no exceptional requirements.

8. SUMMARY OF COMPARATIVE EFFECTIVENESS IN A VARIETY OF CLINICAL SETTINGS

Methoxyflurane is a potent and safe analgesic that is self-administered under observation (and assisted if necessary) using the hand-held Penthrox™ Inhaler. Methoxyflurane is indicated for the relief of pain and provision of analgesia in conscious patients. The settings for the provision of analgesia by Methoxyflurane include pre-hospital, emergency and mass casualty situations, industrial, sporting, and hospital (such as short surgical procedures such as the change of dressings, dislocations and greenstick fractures).

Methoxyflurane belongs to the fluorinated hydrocarbon group of volatile anaesthetics. It is inhaled as a vapour at low (sub-anaesthetic) concentrations, to produce analgesia for the management of moderate to severe pain. It has been used successfully during minor surgical procedures, labour and delivery, dental procedures, and for management of pain in the pre-hospital, military, emergency search and rescue and industrial setting. The range of possible applications for Methoxyflurane, as the analgesic agent for the provision of approximately one hour of effective pain relief, are significant. At the recommended dose, anaesthesia cannot occur.

The hand-held Penthrox™ Inhaler is a small, lightweight, disposable, cylindrical polyethylene device, approximately 15 cm long in a distinctive green colour and effectively looks like a large (green) whistle. At one end is a mouthpiece, near which the design incorporates a diluter hole that, when covered with the patient's index finger, allows a higher concentration of Methoxyflurane to be inhaled. Internally, the device contains a polypropylene S-shaped wick which absorbs the liquid Methoxyflurane. A one-way valve internally, near the base allows air and Methoxyflurane vapour to be inhaled through the wick. The valve closes on expiration to prevent exhalations (containing a mixture of air, Methoxyflurane and CO₂) passing back through the wick and into the atmosphere. A tape is attached to the inhaler to allow provision for support around the patient's wrist. An inlet nipple is provided at the base of the tube to allow simultaneous use of oxygen, as supplementary oxygen is often indicated for patients in severe pain. There is no wasteful vapourisation of the Methoxyflurane and no difference in Methoxyflurane concentration when oxygen is added, as the oxygen tube bypasses the wick. The Penthrox™ Inhaler is a single-patient use device which prevents cross contamination between patients and is easily disposed of after use. An optional Methoxyflurane scavenger attachment with a chamber containing activated carbon adsorber is also available to adsorb exhaled Methoxyflurane vapours in enclosed environments.

Methoxyflurane concentrations of 0.1-0.2% have been recorded with the diluter hole open and 0.2-0.4% with the diluter hole covered. This enables an increased concentration of Methoxyflurane to be inhaled in severe pain. The mouthpiece
can be placed directly into the mouth or a standard oxygen mask can be fitted to enable breathing in and out simultaneously through the nose and mouth. As Methoxyflurane is self administered, the patient maintains control of pain management; a feature this is important in multiple casualty situations.

In Australia, Methoxyflurane was introduced into the Victorian Ambulance Service in 1975 in an in-circuit vaporiser, delivered with oxygen, in closed circuit equipment. In 1980 it was introduced into the West Australian Ambulance service with the Analgizer® device (Abbott Laboratories Inc. USA; an essentially similar device to the Penthrax™ Inhaler), and was progressively taken up in other states and territories. The Penthrax™ Inhaler replaced the Analgizer® in Australia approximately 15 years ago. Methoxyflurane in combination with the Penthrax™ Inhaler is now used by all Australian Ambulance Services, Australian Defence Forces, Emergency Search and Rescue organisations, First-aid officers, Sporting Associations and Primary Industry sites (i.e., mines), and in the Emergency Department of major Australian hospitals where use for analgesia in both children and adults is increasing. The Penthrax™ Inhaler is particularly useful for the administration of analgesia en masse in emergency situations, or to trapped or inaccessible victims (e.g., motor vehicle, mining or cliff accidents). This is due to the continuation of analgesic effectiveness of Methoxyflurane, for several minutes after cessation of administration, combined with the convenience of the Penthrax™ Inhaler.

Of significant note is the application of Methoxyflurane in the provision of effective and safe analgesia to a large number of patients simultaneously (i.e., en masse) in an emergency situation. Examples of these emergency situations include natural disasters (such as earthquakes, landslides, cyclones and floods), mass emergencies (such as transport or industrial accidents), and man-made inflictions (such as wars and terrorism). Stabilisation of the scene of an emergency situation is vital, and the initial management of patients’ pain is of critical importance. Methoxyflurane (administered via the Penthrax™ Inhaler) can be easily administered en masse by trained personnel by simply pouring the liquid Methoxyflurane into the base of the Penthrax™ Inhaler and distributing this to patients for self administration. In comparison to other analgesic alternatives (such as nitrous oxide and parenteral opioids), Methoxyflurane does not require close patient monitoring (i.e., one-on-one supervision). This enables the personnel at the scene of an emergency situation to easily and effectively stabilise patients and organise the consequent stages of emergency response.

In Australia, Methoxyflurane has been used for analgesia for almost thirty years, and the number of administrations now exceeds 2 million. The on-going clinical use of Methoxyflurane for analgesia by health care professionals in Australia is testament to the efficacy of Methoxyflurane to provide effective and potent pain relief.

8.1 Identification of clinical evidence

The available clinical evidence was gained from studies undertaken worldwide, over a period of approximately 45 years, investigating a variety of different outcomes with respect to the ability of Methoxyflurane to provide effective analgesia for moderate to severe pain. Clinical evidence (in the form of papers) that focus on the efficacy of Methoxyflurane for the provision of analgesia total to
5,731 patients (approximately 85% of the total patient numbers reported in the available literature). The weight of evidence supports the efficacy of sub-anaesthetic concentrations of Methoxyflurane for analgesic use.

This proposal has been prepared on the basis of a systematic review of the available clinical literature. Searches of the worldwide literature using Medline (1966 to date), Embase (1974 to date) and the Cochrane Database of Systematic Reviews (2nd Quarter 2004) were last conducted on July 23 2004, July 23 2004 and June 20 2004, respectively. The search strategies employed were kept very broad. In Medline and Embase, search terms were Methoxyflurane as a major topic, restricted to human. The Cochrane Database was searched simply using the term Methoxyflurane.

The following non-eligibility criteria were employed for review of abstracts (or title if no abstract was available) and identification of key papers:

- Not the outcome/indication under review, e.g. Methoxyflurane for use in anaesthesia (proposal based on Methoxyflurane use for analgesia)
- Not the therapeutic under review, e.g. sevoflurane (proposal based on study of Methoxyflurane)
- Not the route of administration under review, e.g. epidural (proposal based on Methoxyflurane for inhalation)
- Not anonymous authors
- Not letters
- Duplicate reference
- Not a journal able to easily obtained through International Inter-library loans

Where it was difficult to assess the suitability of the paper from the abstract (or title), the paper was retrieved for further review against the non-eligibility criteria.

Following initial review against the non-eligibility criteria, 22 non-English papers were identified for further review. In these instances the value of translation was assessed, either by a review of the English abstract, or, where this was not available, a review of the title or a preliminary translation to determine the number of patients and the use of Methoxyflurane. Following initial assessment, two were deemed to add substantially to the body of evidence available in English and were translated.

8.2 Summary of available data

The ability of Methoxyflurane to cause profound analgesia at low (sub-anaesthetic) concentrations is unique. At these concentrations, Methoxyflurane is used for potent analgesia for severe acute pain in conscious patients by self-administration. Methoxyflurane is so potent that it is has been used as the sole agent for analgesia during major abdominal surgery performed while the patient was awake.

The efficacy of inhaled Methoxyflurane as a potent analgesic agent has been demonstrated in a variety of different studies. In a study of Methoxyflurane for conscious analgesia in healthy volunteers, a reduction in pain threshold was seen.
with low blood levels (1.25-4.2 mg/100 mL) in the majority of subjects. In the pre-hospital setting, Methoxyflurane was effective in providing relief of pain associated with limb injury (fractures, sprains, wounds or damage to the soft tissue), chest/abdominal injury or back/spinal injury. In the Emergency Department setting, Methoxyflurane has been reported to be effective for fractures and dislocations awaiting treatment and for acute pain relief in children with upper limb fracture. Methoxyflurane has also been used effectively as an analgesic agent for burns dressings, and for other painful ward procedures in children, and for minor surgical procedures. Methoxyflurane was also effective for simple dental operative procedures. Finally, numerous studies have demonstrated the effectiveness of Methoxyflurane during labour and delivery. Although Methoxyflurane was often used as part of a combination of agents used for pain relief, Methoxyflurane proved effective even when it was the sole medication used to provide analgesia.

The analgesia attributable to Methoxyflurane has been demonstrated to persist for some time after inhalation, as was reinforced in one study (of Methoxyflurane use for burns dressings), by the observation that one patient, a frail elderly lady, sustained a dislocated shoulder but did not complain of pain until some hours after the dressing had finished. In another study of healthy volunteers, the pain threshold remained significantly greater than the control value for 20 minutes after the administration of Methoxyflurane was ceased, again indicating a persistence of effect. Perhaps the most definitive evidence for the persistence of strong analgesia after administration is the study of Methoxyflurane for post-operative analgesia, where Methoxyflurane was administered as a single supervised inhalation, and then the analgesia was compared to that of intramuscular morphine over a period of 2 hours. Of the 40 patients, the number experiencing none to moderate pain was halved over a 2 hour period, but 2 hours later, 40% of patients were still experiencing no pain to moderate pain.

Efficacy in children has been specifically tested and reported in three studies. The first, a double-blind, placebo controlled, randomized clinical trial investigated self-administered Methoxyflurane inhalation (using the Penthrox™ Inhaler) for emergency analgesia in children over 1 year of age. The reduction in pain was significantly greater with Methoxyflurane than the placebo in children with isolated upper limb fractures, but Methoxyflurane did not reduce the pain associated with venipuncture. In a further two studies using Methoxyflurane for analgesia during burns dressings and other painful ward procedures in children, analgesia was good or very good on 71% of occasions, and it was reported to halve the time required for painful procedures in an excellent paper by Firn. Where the method was judged to have a poor effect, it was found that the child was frightened of the mask used with the inhaler and therefore failed to breathe deeply enough to draw sufficient air through the inhaler. In the second report, analgesia was assessed as good or satisfactory on 95% of occasions, with a note that within 3-5 min after starting Methoxyflurane inhalation, the children stopped crying and their emotional tenseness and fear of pain disappeared.

In fifteen studies (three randomised single controlled blind to patient and midwife, six randomised controlled trials and six case series reports), Methoxyflurane was determined to be an effective analgesic for use in obstetrics. Efficacy was comparable to nitrous oxide when the trial design included this agent as a comparator. Efficacy was also comparable to parenteral agents. It should be noted that Methoxyflurane was frequently used in combination with...
other agents, e.g. meperidine, therefore the conclusions drawn relate to a combination of pain relieving agents used.

With regards to the administration of Methoxyflurane, the primary function of any device should be to enable efficient inhalation of Methoxyflurane vapour, while minimizing environmental exposure. The secondary function is to allow control of the dose in terms of the inspired concentration, recognizing that during conscious analgesia, the patient controls the uptake of Methoxyflurane. As supplementary oxygen is often indicated for a patient in severe pain, the device should also allow simultaneous administration of oxygen.

The literature describes different devices for the delivery of Methoxyflurane vapour for analgesic purposes, demonstrating that all the devices used to deliver Methoxyflurane produce effective pain relief (in the majority of patients treated). The Penthrox™ Inhaler incorporates design features which satisfy all the requirements of a device for Methoxyflurane inhalation. The design incorporates a moulded whistle-like mouthpiece, and minimal inspiratory resistance due to the S-shaped wick and large intake port at the base of the device. A diluter hole is located near the mouthpiece which, when covered, allows a higher concentration of Methoxyflurane to be inhaled. A one-way valve which allows the addition of Methoxyflurane into the inhaler onto the wick; closes on expiration to prolong the containment of Methoxyflurane vapour in the inhaler and ensure that Methoxyflurane is not blown into the atmosphere on exhalation. An optional Methoxyflurane scavenger attachment and/or activated carbon absorber is also available for the purpose of removing Methoxyflurane that may be exhaled through the diluter hole. Tape supports the inhaler and allows provision for tying around the patient’s wrist to prevent the device being dropped. An inlet nipple is provided at the base of the tube to allow simultaneous use of oxygen, as supplementary oxygen is often indicated for a patient in severe pain. There is no wasteful vapourisation of the Methoxyflurane and no difference in Methoxyflurane concentration when oxygen is added, as the oxygen tube bypasses the wick. The inhaler is a single patient use device which prevents cross contamination between patients and once finished with, is easily disposed of.

Importantly, a preliminary report of a double blind, placebo controlled randomized clinical trial in emergency analgesia in children older than 5 years, using the Penthrox™ Inhaler for self-administration of Methoxyflurane as proposed by the Applicant, demonstrated that this device delivers Methoxyflurane to produce significant pain relief in children with upper limb fractures. This has been confirmed in the draft manuscript prepared of the full study, in patients as young as 2 years old. A published case study, although presenting information on the use of Methoxyflurane administered via the Penthrox™ Inhaler for a single patient with severe back pain, did include anecdotal references that Methoxyflurane administered via the Penthrox™ Inhaler proved to be a dependable and complication-free analgesic agent for use in the ambulance services.

Although the literature evidence on Methoxyflurane in combination with the Penthrox™ Inhaler is limited, there is considerable evidence on the efficacy of Methoxyflurane in combination with the Analgizer®, an essentially similar device. In studies designed to determine the performance of the Analgizer®, the mean venous blood levels of Methoxyflurane were in the 1-2 mg/100 mL range. The Analgizer® has been used effectively in obstetrics, post-operative...
analgesia\textsuperscript{9,10} for analgesia during burns dressing changes\textsuperscript{11,12}, in the pre-hospital setting\textsuperscript{13} and for minor painful injuries\textsuperscript{14} or surgical procedures,\textsuperscript{15} often using less than 15 mL\textsuperscript{13,15}.

The evidence presented supports the efficacy of the Penthrox\textsuperscript{TM} inhaler for use with Methoxyflurane for conscious analgesia. In conclusion, the available evidence supports the ability of Methoxyflurane, in the proposed dose regimen, administered via the Penthrox\textsuperscript{TM} Inhaler to fulfil the indications sought:

- “Self-administration to conscious patients for the relief of moderate to severe pain, under supervision by personnel trained in its use”, and
- “Monitored conscious patients who require analgesia for the relief of pain in short surgical procedures”

A table that provides a summary of the available literature regarding the use of Methoxyflurane as an effective analgesic is presented in Section 14 – References.

8.3 Summary of available estimates of comparative effectiveness

It is important that analgesic agents used to provide pain relief do not interfere with the patients’ physiological condition, nor the subsequent diagnosis and management when admitted to hospital. The aim of the treatment is to significantly diminish rather than completely abolish the pain to avoid masking acute symptoms when medical help is obtained. The use of Methoxyflurane is therefore preferred in this setting because the dose is self-limiting and the effects are reversible, thus symptoms are not masked. Methoxyflurane does not interfere with other analgesic agents or anaesthetic drugs, therefore does not limit subsequent treatment choices.

Self-administered Methoxyflurane has the ability to produce pain relief equivalent to 10 mg intramuscular morphine (in a standard 70 kg adult), without the respiratory depression associated with the use of an opioid\textsuperscript{9,10}. Methoxyflurane has negligible effects on the cardiovascular system and can be safely administered to patients in shock. In fact, a stabilizing action of Methoxyflurane on cardio-respiratory function has been reported\textsuperscript{37}.

Tomlin et al\textsuperscript{2} compared the sensory effects of Nitrous Oxide and Methoxyflurane. In this study, the only available comparison of the two agents, Methoxyflurane proved to be a much more effective analgesic than nitrous oxide. Subjects inhaling Nitrous Oxide were almost unconscious before any change in the character of painful stimuli was demonstrated and the analgesic effect disappeared rapidly upon recovery. Subjects associated inattention to the painful stimuli (with Nitrous Oxide) with feeling too euphoric to bother about it. In comparison, painful stimuli were felt only as touch very early with Methoxyflurane and analgesia lasted well into the recovery period. Emotional lability appeared to be more reduced with Methoxyflurane in comparison to Nitrous Oxide. Disturbances in taste and nausea were also much less pronounced with Methoxyflurane.
There are several key advantages of Methoxyflurane (administered via the Penthrox™ Inhaler) for use as an analgesic agent:

- Potent analgesic with high percentage of efficacious results
- Non-narcotic, with minimal side effects
- Rapid onset of analgesia, with gradual offset
- Inhaled, with no need for injections or needles (which also removes the possibility of needlestick injury)
- Ease and speed of administration (requires minimal training)
- No effect on patient's vital signs
- Inhaler device is small, lightweight, and allows for easy storage
- Able to be easily administered en masse in emergency situations
- Able to be thrown to inaccessible trauma patients
- Allows the patient the ability to regulate the dose
- Single patient use device prevents the risk of cross contamination and eliminates the need for cleaning and sterilization
- Self-administration by patient is useful in multiple casualty situations
- Retained analgesia is useful when extricating trapped patients
- Can be administered via a facemask and simultaneously with oxygen

In Australia, as a result of its efficacy and safety, the use of Methoxyflurane in combination with the Penthrox™ Inhaler in the pre-hospital setting has become the standard of care in the provision of potent analgesia for acute pain. The Penthrox™ Inhaler provides two concentration levels (0.1-0.2% with the diluter hole open or 0.2-0.4% with the diluter hole closed), which is controlled by the patient. To ensure the Penthrox™ inhaler is not misplaced during intermittent administration, the tape is looped around the wrist. Virenque et al\textsuperscript{37} reported that patients tended to stop taking Methoxyflurane spontaneously as soon as a favourable effect was obtained.

In paediatric patients, intramuscular and intravenous administration of opiates is painful and distressing, particularly to a child who is already in pain, thus the speed of administration, the measure of control afforded the child and the lack of requirement for a needle are of particular benefit.

**Nitrous Oxide**

A 50/50 Nitrous Oxide and oxygen mixture as a pressured gas in a cylinder is also widely believed to be equivalent to 10 mg intramuscular Morphine, although there has not been clinical substantiation of this claim.\textsuperscript{1}

Nitrous Oxide is usually administered using a face mask attached to a demand valve system. A tight fit between the patients face and the mask is required to ensure that any demand valve system functions correctly. The weight and bulk of the equipment present a storage and usage problem, and excludes its use in many circumstances such as car wrecks and cliff injuries when accessibility to the patient is denied. Nitrous Oxide / Oxygen is not flammable but supports combustion more so than oxygen alone and care is required in confined areas such as underground mine situations. In cold conditions (below -6°C), or if a cylinder is required to be stored outside, the gases may separate, thus the cylinder must be inverted and shaken vigorously to ensure adequate mixing. Care is required during cleaning, decontamination and subsequent reassembly to
eliminate the possible transmission of viruses and other organisms between patients. When the cylinder is almost empty, a lower proportion of oxygen may be delivered, therefore cylinders should be refilled when less than 50% full, which is wasteful and expensive.

Nitrous Oxide has low lipid solubility and is rapidly eliminated from the lungs into the environment. When administered for the same time period as 6 mL of Methoxyflurane (approximately 1 hour), 250 L of Nitrous Oxide will be consumed. Almost all of this is excreted through exhalation to the atmosphere. As each mL of Methoxyflurane can vapourise to approximately 200 mL of vapour, the maximum dose represents 1200 mL, with only a proportion escaping to the atmosphere because of the high lipid solubility of Methoxyflurane. Nitrous Oxide represents a pollution factor approximately 200 times that of Methoxyflurane, and initiates concerns about the potential hazards of chronic exposure of operators to Nitrous Oxide. The potential dangers to patients and operators are blood disorders (megaloblastic bone-marrow changes, agranulocytosis), interference with DNA synthesis (possibly explaining the incidence of abortions and foetal abnormalities reported in the literature), and an effect on Vitamin B12 metabolism and the immune system. As Nitrous Oxide is odourless, this factor has been ignored in part, whereas the readily detectable smell of Methoxyflurane ensures the administrator is aware of its presence. Independent studies of the atmospheric concentrations of Methoxyflurane have found that concentrations were within the recommended levels.

Nitrous Oxide's capability of diffusing into gas filled cavities e.g. intestine, thorax and the middle ear, can increase the volume and pressure in these spaces, therefore Nitrous Oxide is contraindicated in patients at risk such as pneumothorax, bowel obstruction, head injuries with impaired consciousness, faciomaxillary injuries and decompression sickness. Changes in middle ear spaces can lead to tinnitus, nausea and vomiting. Depression of myocardial contractility and increased myocardial workload are also known to result from Nitrous Oxide, and this has been associated with an increased mortality rate in patients with coronary artery disease.

Nitrous Oxide has a rapid offset when administration is ceased and severe pain returns quickly. This is a disadvantage when time is required to extricate trapped patients, as well as the effective management of pain in emergency situations. It is not uncommon for Nitrous Oxide to have an aberrant effect, such as severe disorientation and ineffective pain relief.

Parenteral Opioids (e.g. Morphine)

Parenteral administration of opioids is difficult in some circumstances (in trapped or remote situations) and acute symptoms can be masked when subsequent medical help is obtained. Particular care is required to avoid needlestick injuries. Special skills are required for intravenous administration, which is recommended to avoid the delayed ‘rebound’ effect of intramuscular or subcutaneous administration.

Opioids are drugs of addiction, and have been reported to cause addiction even with infrequent administration. The controls associated with assuring the necessary safety and security with these agents mean that use of these agents is often restricted. The adverse effect profile is frequently characterised by
respiratory depression, nausea and vomiting (in up to 1 in 5 cases after intravenous administration), and the medical situations where the use of opioids is contraindicated are considerable. Finally, the use of opioids in the management of pain in a mass casualty and emergency situation is also questionable, as the adverse effect profile for patients as well as the quantity and quality of highly trained personnel required to provide intravenous administration are not favourable.

In conclusion, the weight of clinical evidence confirms that Methoxyflurane is a well-established analgesic agent for patients in need of rapid and potent analgesia. This evidence, combined with approximately 30 years of Methoxyflurane use in Australia (with 15 years experience in combination with the Penthrox™ Inhaler), establishes the efficacy of Methoxyflurane as a potent analgesic agent. When used at the recommended dose with the Penthrox™ Inhaler, the overall efficacy of Methoxyflurane in comparison to other analgesic agents (such as Nitrous Oxide and Morphine) is highly favourable. Furthermore, Methoxyflurane has a remarkable safety profile at the low doses used for analgesia in that minimal side effects have been reported.

9. SUMMARY OF COMPARATIVE EVIDENCE ON SAFETY

Methoxyflurane has been administered as an analgesic agent in Australia since 1975, with over 2 million administrations. During this time only two possible adverse events have been reported, despite Australia having one of the highest spontaneous adverse event reporting rates in the world. In both of these reports, other concomitant medications were more likely to have caused the adverse event.

Published literature and clinical evidence over the past 40 years provides useful data confirming the anticipated adverse effect profile of Methoxyflurane. Importantly there is no evidence of nephrotoxicity associated with sub-anaesthetic doses of Methoxyflurane (even when administered every 1-2 days), and the biochemical evidence demonstrates that the resulting levels of metabolites are well below levels associated with subclinical toxicity.

The Product Information Leaflet that is packaged with Methoxyflurane includes pertinent precautions and warnings, often despite the lack of evidence that these are relevant to the analgesic doses of Methoxyflurane. The adverse effects included in the Product Information leaflet address concerns associated with doses used for anaesthesia. Provided the instructions in the Product Information Leaflet are followed and the precautions and warnings provided are duly noted, there is no reason to believe that the use of Methoxyflurane would be deleterious to the public health.

9.1 Estimate of total patient exposure to date

In Australia, Methoxyflurane has been used for analgesia for almost thirty years and the number of administrations now exceeds 2 million.
9.2 Description of adverse effects / reactions

Since 1975, there have been only two adverse reactions reported to the Australian Therapeutic Goods Administration. The first, made in 1985, was a report of cholestatic hepatitis in a 20 year old male patient; Methoxyflurane was listed as a possible cause, along with halothane, chlorpromazine hydrochloride, meperidine hydrochloride, flucloxacillin sodium, thiopentone sodium, suxamethonium, pancuronium bromide and fentanyl citrate. The second report, made in 2000, was for malignant hyperthermia in a 30 year old male. Methoxyflurane was again listed as a possible cause, along with propofol, suxamethonium and sevoflurane. In each case, the list of suspected agents includes drugs which are more likely to have been the causative agent of the adverse event. In both cases suxamethonium is more likely to have produced the hepatitis is a known trigger for malignant hyperthermia. Although under-reporting in spontaneous pharmacovigilance systems is acknowledged, Australia has one of the best reporting rates in the world, which provides confidence in the safety profile of Methoxyflurane for analgesic purposes.

9.3 Identification of variation in safety due to health systems and patient factors

The use of Methoxyflurane in the provision of analgesia is ‘well-established’ and well documented. Clinical evidence regarding the safety of Methoxyflurane used in sub-anaesthetic concentrations as an analgesic agent in conscious patients has been systematically reviewed.

The published literature provides clinical evidence on Methoxyflurane inhalation in 6,760 patients for analgesic use. Dosage ranged from 0.2% to 0.7%, and included durations of inhalation longer than the 1 hour anticipated duration of the 6 mL of Methoxyflurane when administered via the Penthrox™ Inhaler. The demographics and other characteristics of the total population covered by the published studies encompass the expected population for which Methoxyflurane analgesia is indicated, including paediatric and pregnant patients.

Vital signs

At sub-anaesthetic concentrations, Methoxyflurane has minimal pharmacological effect on vital signs. There is no clinical depression of respiration or circulation and no significant lowering of the blood pressure. In the literature reviewed, there was only one report of Methoxyflurane impacting vital signs (hypotension) which occurred following a surgical procedure for which preoperative medication and another anaesthetic agent were also administered. In another study in emergency analgesia, Methoxyflurane was, in fact, reported to have a stabilizing action on cardiorespiratory function.

Where Methoxyflurane has been used in pregnant women, Methoxyflurane was found to have little effect on the foetus. No foetal complications were reported to result from Methoxyflurane analgesia to the mother in all the studies completed in obstetric analgesia.
Renal

The major concern with Methoxyflurane is nephrotoxicity, which has been reported following anaesthetic use only. These cases occurred when large doses were administered to patients for a prolonged period of time (i.e., hours). Importantly there is **NO** evidence of nephrotoxicity associated with sub-anaesthetic doses of Methoxyflurane (even when administered every 1-2 days). The biochemical evidence demonstrates that when Methoxyflurane is used in sub-anaesthetic concentrations for the provision of analgesia, the resulting levels of metabolites are well below levels associated with subclinical toxicity (and tend to decrease quickly). This is supported by the dosage limits of 6 mL per day and 15 mL per week per patient.

Methoxyflurane nephrotoxicity has been attributed to one of the breakdown products of Methoxyflurane, which includes inorganic fluoride and oxalic acid. Oxalate crystals have been reported in the kidneys following Methoxyflurane nephrotoxicity, however, the degree of oxalate crystal deposition does not adequately explain the development of renal failure. In animal studies, injection of oxalic acid in amounts similar to those resulting from Methoxyflurane did not produce polyuria20 (a key feature of Methoxyflurane nephrotoxicity). The degree of nephrotoxicity can be correlated both with Methoxyflurane dose and the serum inorganic fluoride concentration.21 In animal studies, injection of inorganic fluoride produced renal functional and histological changes similar to those seen following high doses of Methoxyflurane, except that there were no oxalate crystals.20 Thus, it was concluded that inorganic fluoride ions were the prime cause of nephrotoxicity, and that the onset of nephrotoxicity was directly related to the administered dose of Methoxyflurane.

Hepatic

It is suggested, from the evidence presented and the frequency of the reports, that hepatitis is an idiosyncratic response which results from a hypersensitivity reaction.

Abuse

Any volatile compound which will easily vaporize at room temperature, and which has a psychoactive effect and does not produce highly irritating effects can be misused. Methoxyflurane, like other anaesthetic gases and vapours (including Nitrous Oxide) falls into this category. There are no studies specifically investigating the abuse potential of Methoxyflurane.

Chronic Exposure

As Methoxyflurane is not indicated for relief of chronic pain, chronic exposure is most relevant to personnel responsible for Methoxyflurane administration. Chronic exposure to Methoxyflurane has been studied in delivery ward personnel exposed to Methoxyflurane.25,66,67 Methoxyflurane was detected in delivery room air at 0.3-0.8 ppm, alterations in biochemical markers of hepatic and renal function were observed, including an increase in urinary fluoride excretion. The author of these studies suggested a need for scavenging of anaesthetic agents. The optional Methoxyflurane scavenger attachment with a chamber containing activated carbon is available for the purpose of reducing environmental exposure.
to Methoxyflurane, thus minimizing any risk associated with exposure of personnel responsible for the administration of Methoxyflurane.

**Penthrox™ Inhaler – Inhalation Device**

There are no safety concerns in the published literature associated with the use of either the Penthrox™ Inhaler, or its predecessor, the Analgizer®, when used for administration of Methoxyflurane for analgesia.

**Overdose**

Major et al\(^3\) reported that overdose with Methoxyflurane in women in labour could result in the patients becoming sleepy and not easily rousable. In a second study, Major et al\(^4\) investigated varying concentrations of Methoxyflurane for obstetric analgesia. In eight patients given 0.45% Methoxyflurane, five were assessed as very drowsy by the anaesthetist, an opinion confirmed by the midwives (although all patients had also received meperidine).

That renal and hepatic effects are the two major concerns associated with high doses of Methoxyflurane is reinforced by the effects reported in association with Methoxyflurane abuse (hepatitis and renal toxicity). No adverse effects have been reported when Methoxyflurane has been used in sub-anaesthetic concentrations for the provision of analgesia (administered via the Penthrox™ Inhaler in the recommended doses).

**Drug - drug interactions**

There is no evidence in the published literature and there have been no reports of any drug-drug interactions when Methoxyflurane is administered in low (sub-anaesthetic) doses for analgesia.

**Pharmacokinetic and Pharmacodynamic relationship**

The pharmacokinetic and pharmacodynamic profile of Methoxyflurane is eminently suitable for use in sub-anaesthetic concentrations (by inhalation) for the provision of potent analgesia in the treatment of moderate to severe pain. Methoxyflurane is able to provide excellent pain relief, without inducing anaesthesia, at doses which produce metabolites at levels well below the threshold for renal toxicity. Methoxyflurane is rapidly absorbed, so the onset of pain relief is rapid. Further, analgesia is retained for a time after inhalation ceases, an attribute that provides a significant advantage when interruption of administration is necessary (such as in an emergency rescue that requires patient extrication).

In conclusion, a daily maximum of 6 mL of Methoxyflurane may be safely used for the self-administered management of moderate to severe pain by intermittent inhalation via the Penthrox™ Inhaler. The abundance of world-wide clinical evidence and the on-going use in Australia confirms that Methoxyflurane, when used with the Penthrox™ Inhaler according to the stated dose regimen, is very safe and well tolerated.
10. SUMMARY OF AVAILABLE DATA ON COMPARATIVE COST AND COST-EFFECTIVENESS WITHIN THE PHARMACOLOGICAL OR THERAPEUTIC GROUP

The current available prices for Methoxyflurane (administered via the Penthrox™ Inhaler) are as follows:

<table>
<thead>
<tr>
<th>Product</th>
<th>Dosage</th>
<th>Presentation</th>
<th>Quantity</th>
<th>Cost (AUD$)</th>
<th>Cost (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methoxyflurane</td>
<td>1 x 3 mL</td>
<td>Combined with Penthrox™ Inhaler</td>
<td>Pack of 10</td>
<td>$288.55</td>
<td>$215.26</td>
</tr>
<tr>
<td>Methoxyflurane</td>
<td>2 x 3 mL</td>
<td>Combined with Penthrox™ Inhaler</td>
<td>Pack of 10</td>
<td>$411.90</td>
<td>$307.28</td>
</tr>
</tbody>
</table>

Currency conversion rate: US$1.00 = AUD$0.746 (as at 26 October 2004)

10.1 Range of costs of the proposed medicine

Based on the information contained within the above table, the cost per administration of Methoxyflurane is as follows:

Approximately 25 - 30 minutes of analgesia (to children and adults of all ages)
- AUD$28.86 per 1 x 3 mL bottle of Methoxyflurane and Penthrox™ Inhaler
- US$21.53 per 1 x 3 mL bottle of Methoxyflurane and Penthrox™ Inhaler

Approximately 55 - 60 minutes of analgesia (to children and adults of all ages)
- AUD$41.19 per 2 x 3 mL bottle of Methoxyflurane and Penthrox™ Inhaler
- US$30.73 per 2 x 3 mL bottle of Methoxyflurane and Penthrox™ Inhaler

There is only one manufacturer and supplier of Methoxyflurane globally. Therefore, the above information represents the range of costs for the procurement of Methoxyflurane (administered via the Penthrox™ Inhaler).

10.2 Comparative cost-effectiveness presented as a range of cost per routine outcome

A routine outcome has been defined as the provision of approximately 60 minutes of analgesia. While there are no products that are directly similar to Methoxyflurane, Nitrous Oxide / Oxygen and Morphine Sulfate have been used as comparators for the purposes of determining cost-effectiveness.
APPLICATION FOR INCLUSION OF METHOXYFLURANE IN THE
WHO MODEL LIST OF ESSENTIAL MEDICINES

MEDICAL DEVELOPMENTS INTERNATIONAL LIMITED

### Analgesic Company

<table>
<thead>
<tr>
<th>Analgesic Company</th>
<th>Country</th>
<th>Dosage</th>
<th>Cost (AUD$)</th>
<th>Cost (US$)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methoxyflurane</td>
<td>Australia</td>
<td>6 mL</td>
<td>$41.19</td>
<td>$30.73</td>
<td>MIMS</td>
</tr>
<tr>
<td>Medical Developments International Limited</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrous Oxide / Oxygen</td>
<td>Australia</td>
<td>480 L (at flow rate of 8 L/min)</td>
<td>$43.66</td>
<td>$32.57</td>
<td>Supplier</td>
</tr>
<tr>
<td>BOC Limited</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine Sulfate</td>
<td>Australia</td>
<td>20 mg</td>
<td>$18.30</td>
<td>$13.65</td>
<td>MIMS</td>
</tr>
<tr>
<td>Mayne Pharma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Currency conversion rate: US$1.00 = AUD$0.746 (as at 26 October 2004)

### Methodology for calculating costs

**Methoxyflurane**
- Includes the costs for the recommended dosage, as well as the Penthrox™ Inhaler required to administer the analgesic
- The training required to educate personnel on the administration of Methoxyflurane via the Penthrox™ Inhaler is quick and inexpensive

**Nitrous Oxide / Oxygen**
- Includes the costs for the recommended dosage, as well as the cylinder rental costs (favourably assumed to be used 10 times per month) and cylinder delivery costs (favourably assumed to be 5 bottles at a time)
- Does **not** include the costs associated with the procurement of equipment required to administer the analgesic (approximately AUD$1,250.00 / US$932.50 for a Demand Kit)
- Does **not** include the costs associated with the regular servicing of the equipment that is required
- Does **not** include the costs associated with personnel providing constant supervision of the patient’s use of the analgesic

**Morphine Sulfate**
- Includes the costs for the recommended adult dosage, as well as the syringe required to administer the analgesic
- Does **not** include the costs associated with providing personnel with the appropriate training required to administer via a syringe
- Does **not** include the costs associated with personnel providing constant supervision of the patient’s use of the analgesic
- Does **not** include the costs associated with personnel and pharmaceutical products required to counteract adverse reactions
11. SUMMARY OF REGULATORY STATUS OF THE MEDICINE

Registered: Australia, New Zealand
Pending: Iran, Pakistan, Gulf Central Committee for Drug Registration (covers UAE, Saudi Arabia, Kuwait, Oman, Qatar and Yemen)
Proposed*: U.S.A, Canada, Singapore, South Korea, South Africa

* December 2004

12. AVAILABILITY OF PHARMACOPOIEAL STANDARDS

British Pharmacopoeia: No
International Pharmacopoeia: No
United States Pharmacopoeia: Yes

13. PROPOSED TEXT FOR THE WHO MODEL FORMULARY

Description

Methoxyflurane (Inhalation Analgesic) – administered via the Penthrox™ Inhaler.

Presentation

Combination Blister Pack – 1 x 3 mL bottle of Methoxyflurane and 1 x Penthrox™ Inhaler (Pack of 10).

Combination Blister Pack – 2 x 3 mL bottle of Methoxyflurane and 1 x Penthrox™ Inhaler (Pack of 10).

Indications for use

- Self-administration by conscious patients with trauma and associated pain
- Conscious patients who require analgesia for the relief of pain in short surgical procedures

Contraindications

There is no documented evidence of contraindications for the use of Methoxyflurane when administered in sub-anaesthetic concentrations for the provision of analgesia as recommended.

However, contraindications for the use of Methoxyflurane when administered in anaesthetic concentrations are: renal impairment; cardiovascular instability; respiratory depression; head injury; loss of consciousness; toxaemia of pregnancy.

Precautions

There is no documented evidence regarding precautions for the use of Methoxyflurane when administered in sub-anaesthetic concentrations for the provision of analgesia as recommended.
However, precautions for the use of Methoxyflurane when administered in anaesthetic concentrations are: renal impairment; previous liver damage due to Methoxyflurane or Halothane anaesthesia; malignant hypothermia; pregnancy; lactation.

**Dosage**

3 mL of Methoxyflurane provides analgesia for approximately 25 – 30 minutes. Another dose of 3 mL of Methoxyflurane can be subsequently administered to provide analgesia for a further 30 minutes (a total of approximately 55 – 60 minutes).

The total daily dose should not exceed 6 mL of Methoxyflurane per patient. The lowest effective dosage of Methoxyflurane to provide analgesia should be used. The total weekly dose should not exceed 15 mL of Methoxyflurane per patient.

**Administration**

Methoxyflurane is self-administered by the patient (and assisted if necessary). Preparation of the Penthrox™ Inhaler should be performed by a person trained in its use. It is preferable for the person preparing the Penthrox™ Inhaler to supervise the patient’s use of Methoxyflurane. However, in situations where supervision may not be feasible (such as a multi-casualty situation) the patient can self-administer Methoxyflurane without supervision. If preferred, a standard face mask can be attached to the mouthpiece of the Penthrox™ Inhaler. If required, oxygen can be administered simultaneously.

**Adverse reactions**

Methoxyflurane has been administered in sub-anaesthetic concentrations for the provision of analgesia as recommended in Australia since 1975, with over 2 million administrations. During this time only two possible adverse events have been reported, despite Australia having one of the highest spontaneous adverse event reporting rates in the world. In both of these reports, other concomitant medications were more likely to have caused the adverse event.

There are no data on the dose-dependency of the adverse reactions; therefore all of the documented adverse reactions are possible, however no statement regarding frequency can be made.

Adverse reactions from the use of Methoxyflurane when administered in anaesthetic concentrations are:

**Common:** retrograde amnesia; nausea; vomiting; coughing; drowsiness; sleeping; dizziness; dislike of odour; fever; polyuria; headache

**Rare:** non-specific hepatitis; malignant hypothermia

**Other:** respiratory depression; laryngospasm; bronchospasm; cardiac arrest; hypotension; bradycardia; renal failure; increased serum urea; increased serum creatinine; increase urinary oxalate excretion; increased serum inorganic fluoride; pallor; muscle relaxation
14. REFERENCES


McCaskill et al (manuscript in preparation).

Latto IP, Molloy MJ, Rosen M. Changes in arterial blood levels of Methoxyflurane (0.35 per cent inspired vapour concentration) during intermittent patient controlled inhalation in labour. Brit J Anaesth 1971;43(2):201-2.


68 Thomas W. Methoxyflurane, can it be used in the emergency department? AENJ 1997;1(3):13-5.
<table>
<thead>
<tr>
<th>Study Type</th>
<th>Study identifier</th>
<th>Location of study report</th>
<th>Objective/s of the study</th>
<th>Study design and type of control</th>
<th>Test products (dose, route, regimen)</th>
<th>No. of subjects</th>
<th>Diagnosis of subjects</th>
<th>Duration of treatment</th>
<th>Study status: type of report</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Chin et al 2002</td>
<td></td>
<td>Effectiveness of MF for acute pain relief in children &gt; 5 years of age with an upper limb fracture</td>
<td>Randomised double blind placebo controlled</td>
<td>MF or saline (placebo) self-administered via Penthrox inhaler</td>
<td>41 (20 MF)</td>
<td>Children &gt; 5 years of age with an upper limb fracture</td>
<td>U</td>
<td>Abstract Journal publication</td>
<td>The reduction in the total mean pain score in the MF group was significantly (p&lt;0.05) greater than in the placebo group. MF was effective for acute pain relief in children with upper limb fractures.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>McCaskill et al</td>
<td></td>
<td>Effectiveness of MF for acute pain relief in children &gt; 1 year of age with an upper limb fracture or undergoing venipuncture</td>
<td>Randomised double blind placebo controlled</td>
<td>MF or saline (placebo) self-administered via Penthrox inhaler</td>
<td>51 fracture (26 MF 24 saline)</td>
<td>Children &gt; 1 year of age with an upper limb fracture</td>
<td>U</td>
<td>Draft report</td>
<td>MF was effective for early pain relief in children with upper limb fracture. There was no measurable effect on reducing pain and distress associated with venipuncture.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Jones et al 1969 (I)</td>
<td></td>
<td>Comparison of nitrous oxide and MF, administered continuously, as obstetric analgesics</td>
<td>Randomised single controlled blind to patient and midwife</td>
<td>Inhaled MF 0.22% nitrous oxide</td>
<td>48 (24 MF) (24 NO)</td>
<td>Women in labour</td>
<td>Ave durations of inhalation MF 82.5 min (SD±72.7) NO 83 min (SD±66.3)</td>
<td>Complete Journal publication</td>
<td>The anaesthetists’ assessment showed no difference between the mean results, but a greater number of MF patients were satisfactory for 90-100% of the time than the NO patients.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Major et al 1966</td>
<td></td>
<td>Comparison of MF and TCE as obstetric analgesics</td>
<td>Randomised single controlled blind to patient and midwife</td>
<td>Inhaled MF 0.1-1.5% TCE 0.1-1.5%</td>
<td>46 (25 MF) (21 TCE)</td>
<td>Mothers</td>
<td>Ave durations of inhalation MF 1 h 25 min TCE 1 h 17 min</td>
<td>Complete Journal publication</td>
<td>The MF group was satisfactory significantly longer than the TCE group based on anaesthetist assessment. The mothers’ assessment also showed that a significantly higher number of the MF group considered pain relief complete.</td>
</tr>
<tr>
<td>Study Type</td>
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<td>Conclusions</td>
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</tbody>
</table>
| Efficacy   | Major et al 1967 |                          | Effects of MF as an obstetric analgesic when self-administered by intermittent inhalation from a Penlon P.D.V. vaporiser | Randomised single controlled blind to patient and midwife | Inhaled MF 0.35%  
MF 0.25%  | 43  
(23 0.35%)  
(20 0.25%) | Mothers  
Ave durations of inhalation 0.35% 1.5 h  
0.25% 1 h 26 min | Complete Journal publication | The 0.35% group was satisfactory for significantly longer than the 0.25% group. |
| Efficacy   | Yakaitis et al 1972 |                          | MF for effectiveness and patient acceptance in the treatment of post-operative pain | Randomised controlled Single blind | Inhaled MF 15 mL  
morphine 10 mg IM  | 80  
(40 MF)  
(40 morph) | Surgical patients | MF ave duration 6.4 min (1-13 min) | Complete Journal publication | Patients who had received morphine experienced significantly greater pain relief than those who had received MF (p<0.05) |
| Efficacy   | Rosen et al 1969 |                          | Comparison of the effectiveness of MF, nitrous oxide and TCE for the relief of pain in labour | Randomised active controlled | Inhaled MF 0.35% v/v  
NO 50% v/v  | 1,257  
(598 MF)  
(265 NO)  
(394 TCE) | Women in labour | Ave durations of inhalation: MF 91.19 min  
NO 97.15 min | Complete Journal publication | MF gave pain relief comparable to the other agents. |
| Efficacy   | Jones et al 1969 (II) |                          | Comparison of intermittent self-administration of MF and nitrous oxide as obstetric analgesics | Randomised active controlled | Inhaled MF 0.35%  
nitrous oxide 50%  | 50  
(25 MF)  
(25 NO) | Mothers  
U | Complete Journal publication | Objective assessment by an anaesthetist demonstrated that MF was a more effective analgesic than NO, and this was supported by the opinion of the mothers. |
| Efficacy   | Bergsjo et al 1971 |                          | Comparison of 50% nitrous oxide and oxygen with MF for obstetrical analgesia | Randomised controlled cross-over | Inhaled MF 15 mL (0.3-0.8%) for up to 2 h and 50% nitrous oxide | 63 | Women in labour  
U | Complete Journal publication | Both MF and NO gave excellent or good analgesia in 92% of the cases. |
| Efficacy   | Barber et al 1969 |                          | Comparison of MF administered using the Cyprane inhaler with parenteral agents for | Randomised controlled | Inhaled MF 15 mL  | 120  
(60 MF)  
(60 other) | Women in labour | MF 1-5 h | Complete Journal publication | 93% of MF patients experienced good to excellent analgesia in the early stages of labour with |
<table>
<thead>
<tr>
<th>Study Type</th>
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<th>Study status: type of report</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Smith &amp; Moya 1968</td>
<td></td>
<td>Comparison of inhalational analgesia with MF for vaginal delivery, in comparison with nitrous oxide or cyclopropane</td>
<td>Randomised controlled</td>
<td>Inhaled MF 0.2-0.5% NO 25-40%, 1-5% cyclopropane pudendal block</td>
<td>1616</td>
<td>Multiparous women</td>
<td>U</td>
<td>Complete Journal publication</td>
<td>MF compared favourably with NO and cyclopropane; with the same distribution of efficacy of analgesia.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Clark et al 1968</td>
<td></td>
<td>Comparison of MF analgesia and MF anaesthesia in obstetrics</td>
<td>Randomised controlled</td>
<td>Inhaled MF 0.35-1.15% Inhaled MF anaesthesia with 50% NO and MF (≤1.0%) anaesthesia with 50% NO and MF (≤1.0%) alone</td>
<td>94</td>
<td>Women in labour</td>
<td>Inhal 99.9 min</td>
<td>Complete Journal publication</td>
<td>MF was determined to be efficacious for pain relief in all groups.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Edmunds &amp; Rosen 1975</td>
<td></td>
<td>Comparison of the use of 25% nitrous oxide with 0.35% MF in 25 anxious dental patients undergoing</td>
<td>Randomised controlled</td>
<td>Inhaled MF 0.35% NO 22-25%</td>
<td>23</td>
<td>Dental patients</td>
<td>U</td>
<td>Complete Journal publication</td>
<td>The standard of dentistry which could be performed was acceptable in both groups; however NO</td>
</tr>
<tr>
<td>Study Type</td>
<td>Study identifier</td>
<td>Location of study report</td>
<td>Objective/s of the study</td>
<td>Study design and type of control</td>
<td>Test products (dose, route, regimen)</td>
<td>No. of subjects</td>
<td>Diagnosis of subjects</td>
<td>Duration of treatment</td>
<td>Study status: type of report</td>
<td>Conclusions</td>
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</tr>
<tr>
<td>Safety Pharmacology</td>
<td>Clark et al 1979</td>
<td>-</td>
<td>Investigation of the maternal and neonatal inorganic fluoride levels after MF analgesia for labour and delivery</td>
<td>Randomised controlled</td>
<td>MF 15 mL (5:9 on) during labour and 50%NO and 0.35% MF during delivery</td>
<td>21 (11 MF) (10 meper)</td>
<td>Women in labour</td>
<td>U</td>
<td>Complete Journal publication</td>
<td>Plasma inorganic fluoride levels were raised, however none of the values came close to the possible toxic threshold. Inorganic fluoride levels were higher in infants receiving MF than in controls, but the values were consistently lower than corresponding maternal values, with no change in serum chemical values indicative of gross renal dysfunction.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Arozenius et al 1980</td>
<td>-</td>
<td>Comparison of the analgesic effects of MF-nitrous oxide and nitrous oxide alone during labour</td>
<td>Case control</td>
<td>MF 0.1-0.3% in 50% NO 70% NO in O2</td>
<td>133 (74 MF) (49 NO)</td>
<td>Women in labour</td>
<td>U</td>
<td>Complete Journal publication</td>
<td>Parturients who received MF-NO analgesia reported significantly (p&lt;0.05) lower suffering points than parturients who received NO alone.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Yakaitis &amp; Redding</td>
<td>-</td>
<td>Comparison of the ventilatory effects of</td>
<td>Case series Cross over</td>
<td>Inhaled MF 0.5-0.8%</td>
<td>20</td>
<td>Upper abdominal or</td>
<td>U</td>
<td>Complete Journal publication</td>
<td>Self-administered MF had the ability to relieve pain.</td>
</tr>
</tbody>
</table>

116 treatments for conservative dentistry caused significantly less uncooperative behaviour than MF.
<table>
<thead>
<tr>
<th>Study Type</th>
<th>Study identifier</th>
<th>Location of study report</th>
<th>Objective/s of the study</th>
<th>Study design and type of control</th>
<th>Test products (dose, route, regimen)</th>
<th>No. of subjects</th>
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<th>Duration of treatment</th>
<th>Study status: type of report</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety pharmacology</td>
<td>Creasser et al 1974</td>
<td></td>
<td>To study MF metabolism and renal function after MF analgesia during labour and delivery</td>
<td>Case series random selection</td>
<td>Inhaled MF 0.25% or IM analgesics and nitrous oxide</td>
<td>32 (22 MF)</td>
<td>Women in labour and delivery</td>
<td>MF ave duration 127 min (65-240 min)</td>
<td>Complete Journal publication</td>
<td>Serum inorganic fluoride levels were about half those reported to produce subclinical renal dysfunction, and did not reach the reported nephrotoxic level of 80 µmol/L. BUN, serum creatinine, and serum uric acid increased significantly in the mothers, but never exceeded normal values.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Bodley et al 1966</td>
<td></td>
<td>Investigation of obstetric analgesia with MF</td>
<td>Case series</td>
<td>Inhaled MF 0.5%</td>
<td>62</td>
<td>Women in labour</td>
<td>U</td>
<td>Complete Journal publication</td>
<td>Analgesia was obtained rapidly, safely and without side effects.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Fielding et al 1972</td>
<td></td>
<td>To study the self-administration of MF using the Analgizer for providing analgesia for instrumental vaginal deliveries</td>
<td>Case series</td>
<td>MF 15 mL 0.7-0.8%</td>
<td>41</td>
<td>Women requiring instrumental delivery</td>
<td>0-70 min</td>
<td>Complete Journal publication</td>
<td>Where MF was used alone as an analgesic, pain relief was satisfactory in 69% of patients.</td>
</tr>
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<tr>
<td>Efficacy</td>
<td>Marx et al 1969</td>
<td></td>
<td>To study the clinical and biochemical effects of MF self-administered using the Analgizer during labour</td>
<td>Case series</td>
<td>MF 15 mL 0.75-0.85%</td>
<td>14</td>
<td>Women in labour</td>
<td>Self admin 25-210 min (79±16 min) Dr admin 5-55 min (22±4 min)</td>
<td>Complete Journal publication</td>
<td>In all patients the analgesic effect was considered good to excellent.</td>
</tr>
<tr>
<td>Safety and efficacy</td>
<td>Oyama et al 1972</td>
<td></td>
<td>To determine the hormonal effects of MF analgesia administered via the Analgizer</td>
<td>Case series</td>
<td>MF via Analgizer</td>
<td>8</td>
<td>Women in labour</td>
<td>Mean inhalation time 21 min 11 sec (9.5 min-45 min)</td>
<td>Complete Journal publication</td>
<td>Excellent analgesia was reported in 2 patients and good analgesia in the remaining 6 patients. No adverse effect in any patient was found on labour, maternal blood pressure or heart rate, or condition of the neonate at birth.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Romagnoli et al 1970</td>
<td></td>
<td>To study the analgesic effect of MF administered to obstetrics patients</td>
<td>Case series</td>
<td>15 cc MF self-administered via Analgizer</td>
<td>93</td>
<td>Obstetrics patients</td>
<td>15 min-4h (Ave 1 h 19 min)</td>
<td>Complete Journal publication</td>
<td>77.4% of the administrations were successful from an analgesia and clinical perspective.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Virenque et al 1975</td>
<td></td>
<td>The effect of Methoxyflurane analgesia during evacuation of injured persons</td>
<td>Case series</td>
<td>MF 15 mL self-administered via Analgizer</td>
<td>93</td>
<td>Trauma patients</td>
<td>12-40 min</td>
<td>Complete Journal publication</td>
<td>Concluded to be an effective product that limits shock. Very effective analgesia was obtained in 90 cases.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Romagnoli et al 1970</td>
<td></td>
<td>Use of the Analgizer in the emergency department for patients with fractures and dislocations awaiting treatment</td>
<td>Case study</td>
<td>15 cc MF self-administered via Analgizer</td>
<td>11</td>
<td>Patients with fractures and dislocations</td>
<td>15 min to 2 h (ave = 54 min)</td>
<td>Complete Journal publication</td>
<td>Eight cases (72%) were successes from a clinical perspective, with the Analgizer providing satisfactory analgesia</td>
</tr>
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<tr>
<td>Efficacy</td>
<td>Firn 1972</td>
<td></td>
<td>Use of MF administered via a Cardiff inhaler, as an analgesic for burns dressings and other painful ward procedures in children</td>
<td>Case series</td>
<td>Inhaled MF 0.35±0.07%</td>
<td>36</td>
<td>19 burns patients, 12 plastic surgery and 5 general surgery</td>
<td>Intermittent 1-13 times for 10 min-2.5 h</td>
<td>Complete Journal publication</td>
<td>The use of MF with the Cardiff inhaler was reported to halve the time required for painful procedures.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Marshall &amp; Ozorio 1972</td>
<td></td>
<td>The effectiveness of MF in air, self-administered using a Pentec vaporiser (Cyprane) as the sole inhalational analgesic in the dressing of 60 burns</td>
<td>Case series</td>
<td>Inhaled MF 0.5-0.7%</td>
<td>10</td>
<td>Burn patients</td>
<td>U</td>
<td>Complete Journal publication</td>
<td>In 55 of 60 dressings (90%), analgesia was assessed by the observing anaesthetist as “good” or “very good”</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Packer &amp; Titel 1969</td>
<td></td>
<td>The effectiveness of MF self-administered via the Analgizer for burns dressings on sixty occasions</td>
<td>Case series</td>
<td>Inhaled MF 15 mL ≤0.8%</td>
<td>11</td>
<td>Burn patients</td>
<td>U</td>
<td>Complete Journal publication</td>
<td>8 patients reported good to very good analgesia over the number of dressing changes required.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Packer 1972</td>
<td></td>
<td>The use of MF, administered via either the Analgizer or a Cyprane vapouriser, on 406 consecutive occasions to 88 patients (4 mths – 82 yrs)</td>
<td>Case series</td>
<td>Inhaled MF 0.3-0.8% (15 mL) or 0.1-1.0%</td>
<td>88</td>
<td>Patients in the burns unit</td>
<td>U</td>
<td>Complete Journal publication</td>
<td>Two effects of MF are reported – analgesic properties and mood-modifying effects, taking the form of sedation, dissociation from the surroundings or amnesia. Following this project, MF was reported to be the analgesic of choice in the Burns Unit where the study was carried out.</td>
</tr>
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<tr>
<td>Efficacy and safety</td>
<td>Aleksandrin et al 1976</td>
<td></td>
<td>The effectiveness of MF self-administered via the Cyprane inhaler for burns dressings on 118 occasions in 33 children (2-15 yrs) and the effect of renal and liver biochemistry in 13 children</td>
<td>Case series</td>
<td>Inhaled MF 0-0.6%</td>
<td>33</td>
<td>Burns patients</td>
<td>15-35 min (average) Up to 1 hr reported</td>
<td>Complete Journal Article and English Translation</td>
<td>The effect of MF in children with burns was deemed to be good (complete psychological and physical relaxation in the absence of a response to pain) in 88 cases (75%), and satisfactory in 24 cases (20%)</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Josephson &amp; Schwartz 1974</td>
<td></td>
<td>MF 0.35% in air, administered via the Cardiff inhaler to patients attending for dental treatment.</td>
<td>Case series</td>
<td>Inhaled MF 0.35%</td>
<td>248</td>
<td>Dental patients</td>
<td>U</td>
<td>Complete Journal publication</td>
<td>MF analgesia is adequate for a large variety of simple tasks such as shallow cavities, subgingival curettage, root planning and cementation, but supplemental local anaesthesia is necessary for more painful procedures.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Dragon &amp; Goldstein 1967</td>
<td></td>
<td>The use of MF administered via a Cyprane inhaler for routine dental operative procedures or simple extractions</td>
<td>Case series</td>
<td>Inhaled MF 15 mL</td>
<td>262</td>
<td>Dental patients</td>
<td>U</td>
<td>Complete Journal publication</td>
<td>Good results (patient acceptance of dental procedures) were obtained with 95.4% of the adults, 91.6% of the teenagers, but only 27.2% of the children under 10 years of age.</td>
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<tr>
<td><strong>Efficacy</strong></td>
<td>Reier 1970</td>
<td></td>
<td>Evaluation of Stage I analgesia in patients scheduled for various minor surgical procedures</td>
<td>Case series</td>
<td>Inhaled MF</td>
<td>43</td>
<td>Surgical patients</td>
<td>U</td>
<td>Complete Journal publication</td>
<td>In the patients’ subjective evaluation, amnesia was uniformly complete in most cases. In those patients in whom amnesia was not complete, the analgesia was complete in all except 5 cases</td>
</tr>
<tr>
<td><strong>Safety pharmacology</strong></td>
<td>Palahniuk</td>
<td></td>
<td>Plasma fluoride levels following obstetric use of MF</td>
<td>Case series</td>
<td>MF 0.2-0.5% in 50-70% NO for delivery</td>
<td>106</td>
<td>Women in labour</td>
<td>19.7±5.9 min</td>
<td>Complete Journal publication</td>
<td>There was a statistically significant rise in plasma inorganic fluoride at all times in each group. Mean plasma fluoride levels in all groups of patients studied were well below the levels expected to produce renal impairment</td>
</tr>
<tr>
<td></td>
<td>and Cumming 1975</td>
<td></td>
<td></td>
<td></td>
<td>MF 0.2-0.5% in 50-70% NO for delivery and for labour</td>
<td>106 (50 deliv)</td>
<td>Women in labour</td>
<td>49.1±23.9 min</td>
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<td>MF 0.2-0.5% in 50-70% NO for c section anaesthesia</td>
<td>106 (50 deliv)</td>
<td>Women in labour</td>
<td>39.6±14.2 min</td>
<td></td>
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<td></td>
<td>MF 0.2-0.5% in 50-70% NO for delivery and labour twins</td>
<td>106 (50 deliv)</td>
<td>Women in labour</td>
<td>105 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Rosen et al 1972</td>
<td></td>
<td>The evaluation of kidney function after MF analgesia during labour</td>
<td>Case series</td>
<td>Inhaled MF 0.35% NO 50%</td>
<td>50</td>
<td>Women in labour</td>
<td>U</td>
<td>Complete Journal publication</td>
<td>The results suggest that MF is not nephrotoxic when used as a self-administered analgesic.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Inhaled MF 0.35% NO 50%</td>
<td>200</td>
<td>Women in labour</td>
<td>U</td>
<td>Complete Journal publication</td>
<td>No significant differences between blood urea measurements and urinary/blood urea ratios on the day of discharge between treatment groups</td>
</tr>
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<td></td>
<td>Inhaled MF 0.35% NO 50%</td>
<td></td>
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<td>Complete Journal publication</td>
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<tr>
<td>Safety pharmacology</td>
<td>Dahlgren 1978</td>
<td></td>
<td>Evaluation of urinary fluoride concentration in mothers and neonates after MF-nitrous oxide analgesia during labour</td>
<td>Case series</td>
<td>Inhaled MF/NO up to 10 mL</td>
<td>21 (15 MF)</td>
<td>Women in labour</td>
<td>U</td>
<td>Complete Journal publication</td>
<td>Both the mothers and neonates showed a significantly higher urinary fluoride ion concentration in comparison to NO only patients. The urinary fluoride concentration was demonstrated to be related to the dose of MF administered.</td>
</tr>
<tr>
<td>Safety pharmacology</td>
<td>Dahlgren 1977</td>
<td></td>
<td>Evaluation of the influence of 0-0.3% MF-nitrous oxide analgesia during childbirth on both renal and hepatic function</td>
<td>Case series</td>
<td>Inhaled MF 0-0.3%</td>
<td>201 (126 MF)</td>
<td>Women in labour</td>
<td>U</td>
<td>Complete Journal publication</td>
<td>Of the tests carried out, serum sodium, creatinine, uric acid, urea, glutamic oxaloacetic transaminase (g.o.t.) and glutamic pyruvate transaminase increased following exposure to MF.</td>
</tr>
<tr>
<td>Safety pharmacology</td>
<td>Cuassay et al 1977</td>
<td></td>
<td>To study inorganic fluoride levels in 46 parturients and neonates following MF analgesia during labour and delivery</td>
<td>Case series</td>
<td>Inhaled MF 0.35% during labour and MF/NO 50:50 during delivery</td>
<td>46 (36 MF)</td>
<td>Women in labour and delivery</td>
<td>0.35% MF ave duration 104.8 min and MF/NO ave duration 22.9 min</td>
<td>Complete Journal publication</td>
<td>The levels of serum inorganic fluoride rose to levels below half the reported adult subclinical toxicity values. High maternal fluoride levels are reflected in neonatal levels, however no clinical evidence of renal toxicity was observed.</td>
</tr>
</tbody>
</table>
## Study Details

<table>
<thead>
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<tbody>
<tr>
<td>Safety pharmacology</td>
<td>Clark et al 1976</td>
<td></td>
<td>Investigate the maternal and neonatal inorganic fluoride levels after MF analgesia for labour and delivery</td>
<td>Case series</td>
<td>Inhaled MF 0.3% (1.1-18.2 mL)</td>
<td>50</td>
<td>Women in labour and delivery</td>
<td>Ave duration 139 min (13-375 min)</td>
<td>Complete Journal publication</td>
<td>Renal function, as measured by BUN and creatinine remained essentially within normal limits. It was concluded that MF can be safely administered as a means of providing analgesia during delivery.</td>
</tr>
<tr>
<td>Safety pharmacology</td>
<td>Young et al 1976</td>
<td></td>
<td>Investigation of MF biotransformation and renal function following MF administration for vaginal delivery or Caesarean section</td>
<td>Case series</td>
<td>MF 0.2-0.5% delivery MF in 60% NO for C-section</td>
<td>18 (11 deliv) (7 c-sect)</td>
<td>Women in labour and delivery</td>
<td>Ave duration delivery 23 min (5-70min) c-sect 44 min (25-70 min)</td>
<td>Complete Journal publication</td>
<td>The data indicated that hazardous elevations of serum ionic fluoride with subsequent renal dysfunction are unlikely following low dose MF administration.</td>
</tr>
<tr>
<td>Safety pharmacology</td>
<td>Laird &amp; Chrystal 1972</td>
<td></td>
<td>Renal function following MF analgesia for burns dressings</td>
<td>Case series</td>
<td>Inhaled MF</td>
<td>12</td>
<td>Burns patients</td>
<td>U</td>
<td>Complete Journal publication</td>
<td>Small increases in uric acid were observed in all patients and four patients had small but consistent increases in BUN and serum creatinine. In only one patient were levels of serum uric acid recorded that were greater than accepted normal limits.</td>
</tr>
<tr>
<td>Safety</td>
<td>Rosen et al 1974</td>
<td></td>
<td>Clinical and laboratory investigations for urolithiasis on women who had inhaled MF 0.35% intermittently for more than 1 hour during labour</td>
<td>Case series</td>
<td>Inhaled MF 0.35% for &gt; 1h</td>
<td>32</td>
<td>Women in labour</td>
<td>&gt; 1 hour</td>
<td>Complete Journal publication</td>
<td>The evidence does not suggest that there is a long term risk to the kidneys when 0.35% MF is used for obstetric analgesia</td>
</tr>
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<tr>
<td>Pharmacology</td>
<td>Latto et al 1972</td>
<td></td>
<td>Investigation of changes in arterial blood levels of MF during intermittent patient controlled inhalation</td>
<td>Case series</td>
<td>Inhaled MF 0.35%</td>
<td>16</td>
<td>Mothers</td>
<td>Mean duration of inhalation 77.6 min (13.4-240 min)</td>
<td>Complete Journal publication</td>
<td>The analgesic blood levels reported are much lower than those providing anaesthesia. None of the cases showed a statistically significant rise in blood level over time.</td>
</tr>
<tr>
<td>Pharmacology</td>
<td>Latto et al 1971</td>
<td></td>
<td>Investigation of changes in arterial blood levels of MF during intermittent patient controlled inhalation</td>
<td>Case series</td>
<td>Inhaled MF 0.35%</td>
<td>16 (same patients as Latto et al 1972)</td>
<td>Mothers</td>
<td>U</td>
<td>Complete Journal publication</td>
<td>The analgesic blood levels reported are much lower than those providing anaesthesia. None of the cases showed a statistically significant rise in blood level over time.</td>
</tr>
<tr>
<td>Safety pharmacology</td>
<td>Clark et al 1970</td>
<td></td>
<td>Investigation of the effect of MF on the foetus</td>
<td>Case series</td>
<td>Inhaled MF 0.35-1.15% during labour only</td>
<td>64 (17 MF)</td>
<td>Women in labour</td>
<td>MF mean duration 68.1 min</td>
<td>Complete Journal publication</td>
<td>It was demonstrated that there was no increase in MF blood levels with increased duration of inhaler use, apparently due to the absence of pain-induced hyperventilation.</td>
</tr>
<tr>
<td>Safety pharmacology</td>
<td>Clark et al 1970</td>
<td></td>
<td>Investigation of the effect of MF on the foetus</td>
<td>Case series</td>
<td>MF 0.35-1.15% during labour plus 0.2-0.8% MF/NO during delivery</td>
<td>64 (17 MF)</td>
<td>Women in labour</td>
<td>MF and MF/NO 156.6 min</td>
<td>Complete Journal publication</td>
<td>It was demonstrated that there was no increase in MF blood levels with increased duration of inhaler use, apparently due to the absence of pain-induced hyperventilation.</td>
</tr>
<tr>
<td>Safety pharmacology</td>
<td>Clark et al 1970</td>
<td></td>
<td>Investigation of the effect of MF on the foetus</td>
<td>Case series</td>
<td>No analgesia during labour and 0.2-0.8% MF/NO during delivery</td>
<td>No analgesia during labour and 0.2-0.8% MF/NO during delivery</td>
<td>Women in labour</td>
<td>MF/NO 6.7 min</td>
<td>Complete Journal publication</td>
<td>It was demonstrated that there was no increase in MF blood levels with increased duration of inhaler use, apparently due to the absence of pain-induced hyperventilation.</td>
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<tr>
<td>Safety</td>
<td>McGranahan 1967</td>
<td></td>
<td>The use of intermittent obstetric analgesia using MF, nitrous oxide and oxygen</td>
<td>Case series</td>
<td>Inhaled 0.3-0.4% MF in 50% NO</td>
<td>144</td>
<td>Obstetrics patients</td>
<td>Ave time inhalation 19 min (3-85 min)</td>
<td>Complete Journal publication</td>
<td>Only six patients (4.3%) suffered nausea or vomiting when those with prior vomiting and the patients who received intravenous meperidine and ergotrate were eliminated. No maternal or foetal complications were reported.</td>
</tr>
<tr>
<td>Safety</td>
<td>Lindblad et al 1992</td>
<td></td>
<td>Maternal and perinatal risk factors for Wilms tumor</td>
<td>Cohort study Nested case control</td>
<td>n/a</td>
<td>110</td>
<td>Mothers</td>
<td>n/a</td>
<td>Complete Journal publication</td>
<td>A tentative association between Wilms tumor and MF was reported. It needed further confirmation.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Siker et al 1967</td>
<td></td>
<td>To measure the pain threshold vs blood level of MF</td>
<td>Volunteers served as their own controls</td>
<td>MF (0.3-0.4%)</td>
<td>20</td>
<td>Healthy volunteers</td>
<td>MF 40 min</td>
<td>Complete Journal publication</td>
<td>A reduction in pain threshold was seen with low blood levels (1.25-4.2 mg/100 mL) in the majority of subjects.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Lewis, L 1984</td>
<td>Use of self administered MF for office surgery (hair transplants, dermabrasion, extended flaps and grafts)</td>
<td>Case report</td>
<td>MF 3-5 mL</td>
<td>Approx 4 per week for 15 years</td>
<td>office surgery eg hair transplants, dermabrasion, extended flaps and grafts</td>
<td>U</td>
<td>Complete Journal publication</td>
<td>Use of MF was considered effective and safe.</td>
<td></td>
</tr>
<tr>
<td>Study Type</td>
<td>Study identifier</td>
<td>Location of study report</td>
<td>Objective/s of the study</td>
<td>Study design and type of control</td>
<td>Test products (dose, route, regimen)</td>
<td>No. of subjects</td>
<td>Diagnosis of subjects</td>
<td>Duration of treatment</td>
<td>Study status: type of report</td>
<td>Conclusions</td>
</tr>
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<tr>
<td>Pharmacology</td>
<td>Komesaroff, D 1979</td>
<td></td>
<td>The serum fluoride ion levels in patients with severe pain after MF administration</td>
<td>Case study, random patients</td>
<td>Average – 1.8 mL MF (3 mL maximum)</td>
<td>11</td>
<td>Broken bones (8 patients), Back injury (2 patients), abdominal pain (1 patient)</td>
<td>3-58 min</td>
<td>Journal paper</td>
<td>The serum fluoride ion concentration ranged from 2.0-22.0 µmol/L, with a mean of 12.2 µmol/L.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Hodgkinson 1997</td>
<td></td>
<td>The effect of MF administered by the Penthrox inhaler to a patient with severe back pain</td>
<td>Case report</td>
<td>MF 3 mL</td>
<td>1</td>
<td>Severe back pain</td>
<td>35 min</td>
<td>Case report</td>
<td>MF inhalation provided significant relief of the pain</td>
</tr>
<tr>
<td>Safety</td>
<td>Delia et al 1983</td>
<td></td>
<td>MF hepatitis following obstetric analgesia</td>
<td>Case report</td>
<td>Inhaled MF</td>
<td>2</td>
<td>Women in labour</td>
<td>2 h 20 min and 3.5 h</td>
<td>Case report</td>
<td>Both patients recovered without further complication.</td>
</tr>
<tr>
<td>Safety</td>
<td>Rubinger et al 1975</td>
<td></td>
<td>MF hepatitis following obstetric analgesia</td>
<td>Case report</td>
<td>Inhaled 0.35% MF</td>
<td>1</td>
<td>Woman in labour</td>
<td>U</td>
<td>Case report</td>
<td>The course of the illness was subsequently uneventful, with complete resolution of all abnormalities.</td>
</tr>
<tr>
<td>Safety</td>
<td>Calverley 1972</td>
<td></td>
<td>Polyuria and MF</td>
<td>Case report</td>
<td>Inhaled MF</td>
<td>1</td>
<td>Burns patient</td>
<td>12 of 30 min duration each</td>
<td>Case report</td>
<td>The polyuria was linked to MF, as there was no evidence of any renal or other cause of this problem.</td>
</tr>
</tbody>
</table>

U = unknown  
TCE = trichloroethylene  
NO = nitrous oxide  
MF = Methoxyflurane  
HT = halothane