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NDA 20478

ULTANE

1 OF 4

NDA 20478

UCK+RANE



NDA 20-478

Food and Drug Administration  
Rockville MD 20857

JUN 7 1995

Abbott Hospital Products Division  
Abbott Laboratories  
D-389, Bldg. AP30  
200 Abbott Park Road  
Abbott Park, Illinois 60064-3537

Attention: Mr. Frederick A. Gustafson  
Director, Regulatory Affairs

Dear Mr. Gustafson:

Please refer to your July 8, 1994, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ultane (sevoflurane) Volatile Liquid for Inhalation, 250 mL.

We acknowledge receipt of 28 amendments listed (see enclosed list).

This new drug application provides for the use of Ultane in the induction and maintenance of general anesthesia in adult and pediatric patients for inpatient and outpatient surgery.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this marked-up draft labeling may render the product misbranded and an unapproved new drug.

Please submit fifteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-478. Approval of this labeling by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

NDA 20-478

Page Two

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Pilot Drug Evaluation Staff and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration  
Division of Drug Marketing, Advertising, and Communications, HFD-240  
5600 Fishers Lane  
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may be identified.

We also acknowledge your March 21, 1995 letter, which included the following Phase 4 commitments:

1. To perform a non-human primate study to develop additional information on Compound A.
2. To evaluate the effect of sevoflurane in patients with renal insufficiency.
3. To evaluate the effect of sevoflurane when used in a low flow (< 2 liters/minute) system.

Please submit protocols for these studies as soon as possible. We encourage you to consult with our Division of Biopharmaceutics on the design of the protocol for the study of renally-impaired patients. The original copy of the Phase 4 study protocols and reports should be submitted to this division, with a copy to the Division of Drug Information Resources, HFD-80. Since that division is responsible for tracking Phase 4 studies, a copy of all future communications regarding the Phase 4 studies should also be sent to them.

Please submit one market package of the drug product when it is available.

Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. Within the next month, you will receive an invoice for the amount due. Payment will be due within 30 days of the date of the invoice.

Page Three

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

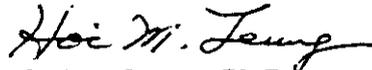
If you have any questions, please contact Millie Wright, Project Manager at (301) 443-3741.

Sincerely yours,

Review Team  
Pilot Drug Evaluation Staff, HFD-007  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research



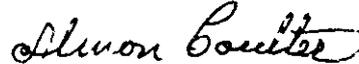
Robert F. Bedford, M.D.  
Acting Director



Hoi M. Leung, Ph.D.  
Statistician



Anwar Goheer, Ph.D.  
Pharmacologist



Almon Coulter, Ph.D.  
Pharmacologist



Juanita Ross, M.S.  
Chemist



Peter Lockwood, M.S.  
Pharmacokineticist

ENCLOSURES (2): List of Amendments  
Draft Labeling

Genol Version 16/95

COPY

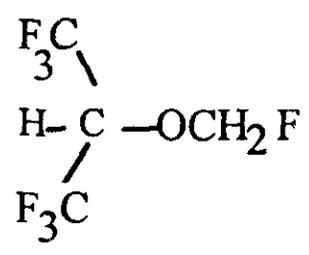
# ULTANE™

(sevoflurane)

volatile liquid for inhalation.

## DESCRIPTION

ULTANE™ (sevoflurane), Volatile Liquid for Inhalation, a nonflammable and nonexplosive liquid administered by vaporization, is a halogenated general inhalation anesthetic drug. Sevoflurane is fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl) ethyl ether and its structural formula is:



### Sevoflurane Physical Constants are:

Molecular weight	200.05
Boiling Point at 760 mm Hg	58.6 °C
Specific gravity at 20°C	1.520 - 1.525
Vapor pressure in mm Hg	157 mm Hg at 20 °C
	197 mm Hg at 25 °C
	317 mm Hg at 36 °C

### Distribution Partition Coefficients at 37 °C:

Blood/Gas	0.63 - 0.69
Water/Gas	0.36
Olive Oil/Gas	47 - 54
Brain/Gas	1.15

### Mean Component/Gas Partition Coefficients at 25 °C for polymers used commonly in medical applications:

Conductive rubber	14.0
Butyl rubber	7.7
Polyvinyl chloride	17.4
Polyethylene	1.3

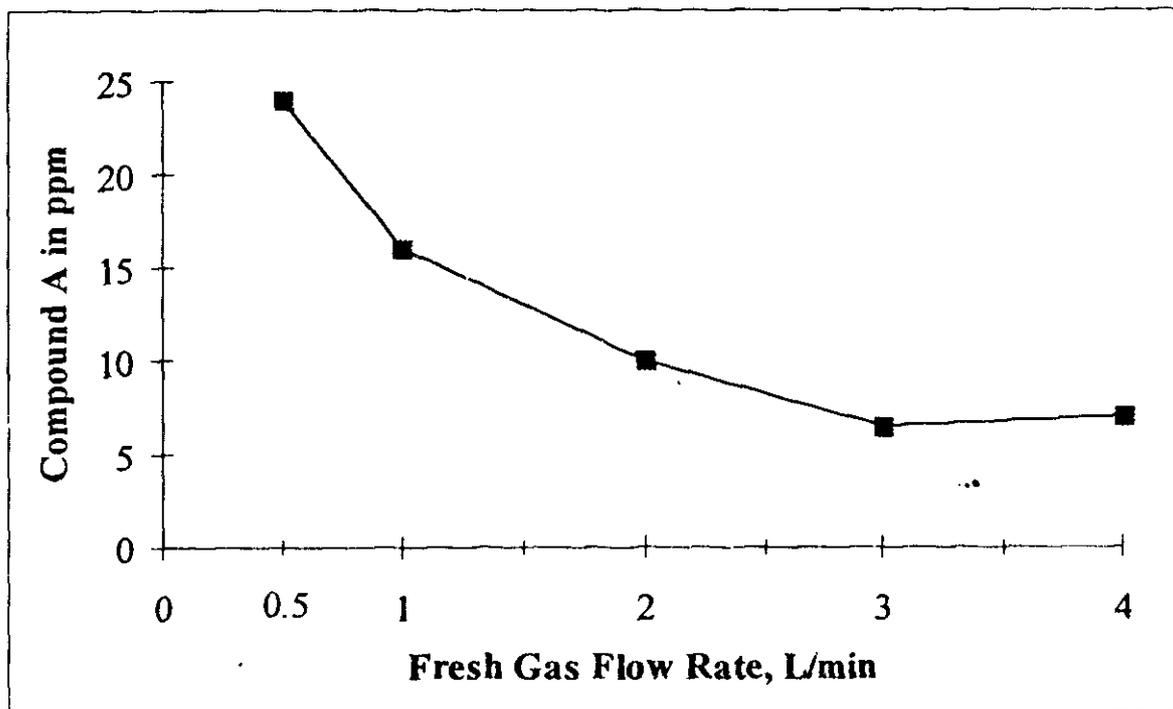
Sevoflurane is nonflammable and nonexplosive as defined by the requirements of International Electrotechnical Commission 601-2-13.

Sevoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Sevoflurane is nonpungent. It is miscible with ethanol, ether, chloroform and petroleum benzene, and it is slightly soluble in water. Sevoflurane is stable when stored under normal room lighting conditions according to instructions.

Sevoflurane is chemically stable. No discernible degradation occurs in the presence of strong acids or heat. The only known degradation reaction in the clinical setting is through direct contact with CO<sub>2</sub> absorbents (soda lime and Baralyme®) producing pentafluoroisopropenyl fluoromethyl ether, (PIFE, C<sub>4</sub>H<sub>2</sub>F<sub>6</sub>O), also known as Compound A, and trace amounts of pentafluoromethoxy isopropyl fluoromethyl (PMFE, C<sub>5</sub>H<sub>6</sub>F<sub>6</sub>O), also known as Compound B.

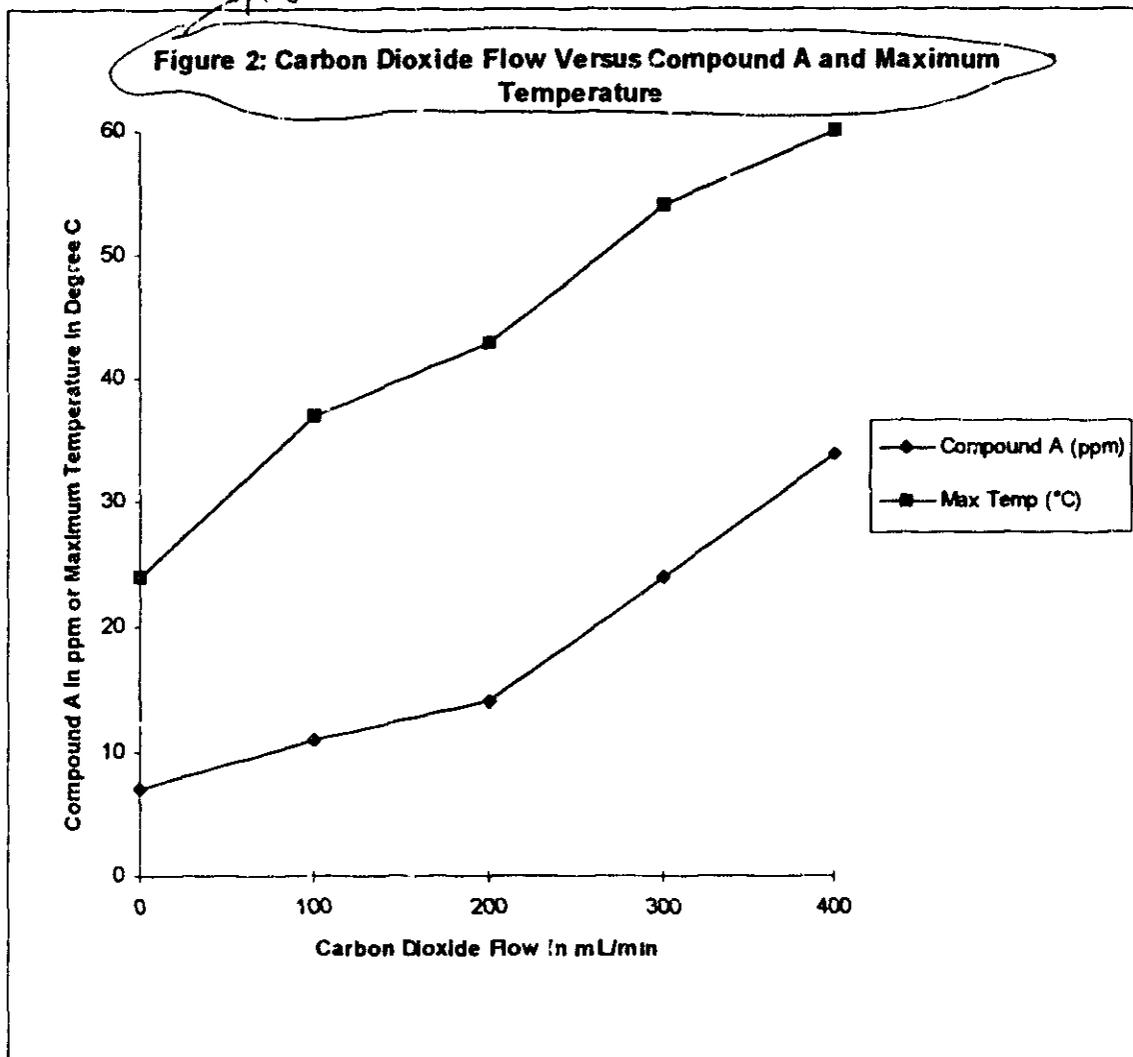
The production of degradants in the anesthesia circuit results from the extraction of the acidic proton in the presence of a strong base (KOH and/or NaOH) forming an alkene (Compound A) from sevoflurane similar to formation of 2-bromo-2-chloro-1,1-difluoro ethylene (BCDFE) from halothane. Baralyme® causes more production of Compound A than does soda lime. Laboratory simulations have shown that the concentration of these degradants are inversely correlated with the fresh gas flow rate (See Figure 1).

Figure 1: Fresh Gas Flow Rate versus Compound A levels in a Circle Absorber System



Sevoflurane degradation in soda lime has been shown to increase with temperature. Since the reaction of carbon dioxide with absorbents is exothermic, this temperature increase will be determined by quantities of CO<sub>2</sub> absorbed, which in turn will depend on fresh gas flow in the anesthesia circle system, metabolic status of the patient, and ventilation. The relationship of temperature produced by varying levels of CO<sub>2</sub> and Compound A production is illustrated in the following in-vitro simulation where CO<sub>2</sub> was added to a circle absorber system.

*move outside.*      *2 ppm CO<sub>2</sub> results in change in FPL*



Compound A has been shown to be nephrotoxic in rats after exposures that have varied in duration from one to three hours. No histopathologic change was seen at a concentration of up to 270 ppm for one hour. Sporadic single cell necrosis of proximal tubule cells has been reported at a concentration of 114 ppm after a 3-hour exposure to Compound A in rats. The LC<sub>50</sub> reported at 1 hour is 1050-1090 ppm (male-female) and, at 3 hours, 350-490 ppm (male-female).

At a fresh gas flow rate of 1 L/min, mean maximum concentrations of Compound A in the anesthesia circuit in clinical settings are approximately 20 ppm (0.002%) with soda lime and 30 ppm (0.003%) with Baralyme® in adult patients; mean maximum concentrations in pediatric patients with soda lime are about half those found in adults. The highest concentration observed in a single patient with Baralyme® was 61 ppm (0.0061%) and 32 ppm (0.0032%) with soda lime. The concentrations of Compound A measured in the anesthesia circuit when sevoflurane is used clinically are not known to be deleterious to humans.

Sevoflurane is not corrosive to stainless steel, brass, aluminum, nickel-plated brass, chrome-plated brass or copper beryllium.

no need brom 4g  
no need brom 4g  
4/16/95 label  
6/2/95 label

### CLINICAL PHARMACOLOGY

Sevoflurane is an inhalational anesthetic agent for use in induction and maintenance of general anesthesia. Minimum alveolar concentration (MAC) of sevoflurane in oxygen for a 40 year old adult is 2.1%. The MAC of sevoflurane decreases with age. (See DOSAGE AND ADMINISTRATION for details).

#### Pharmacokinetics

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no need brom 5g  
4/16/95 label  
6/2/95 label

#### Uptake and distribution

##### Solubility

Because of the low solubility of sevoflurane in blood (blood/gas partition coefficient @ 37°C = 0.63-0.69), a minimal amount of sevoflurane is required to be dissolved in the blood before the alveolar partial pressure is in equilibrium with the arterial partial pressure. Therefore there is a rapid rate of increase in the alveolar (end-tidal) concentration ( $F_A$ ) toward the inspired concentration ( $F_I$ ) during induction.

##### Induction of anesthesia

In a study in which seven healthy male volunteers were administered 70%N<sub>2</sub>O/30%O<sub>2</sub> for 30 minutes followed by 1.0% sevoflurane and 0.6% isoflurane for another 30 minutes the  $F_A/F_I$  ratio was greater for sevoflurane than isoflurane at all time points. The time for the concentration in the alveoli to reach 50% of the inspired concentration was 4-8 minutes for isoflurane and approximately 1 minute for sevoflurane.

$F_A/F_I$  data from this study were compared with  $F_A/F_I$  data of other halogenated anesthetic agents from another study. When all data were normalized to isoflurane, the uptake and distribution of sevoflurane was shown to be faster than isoflurane and halothane, but slower than desflurane. The results are depicted in

~~Figure 2~~ no change

##### Recovery from anesthesia

The low solubility of sevoflurane facilitates rapid elimination via the lungs. The rate of elimination is quantified as the rate of change of the alveolar (end-tidal) concentration following termination of anesthesia ( $F_A$ ), relative to the last alveolar concentration ( $F_{A_0}$ ) measured immediately before discontinuance of the anesthetic. In the healthy volunteer study described above, rate of elimination of sevoflurane was similar compared with desflurane, but faster compared with either halothane or isoflurane. These results are depicted in Figure 4.

Figure 3. Ratio of concentration of anesthetic in alveolar gas to inspired gas

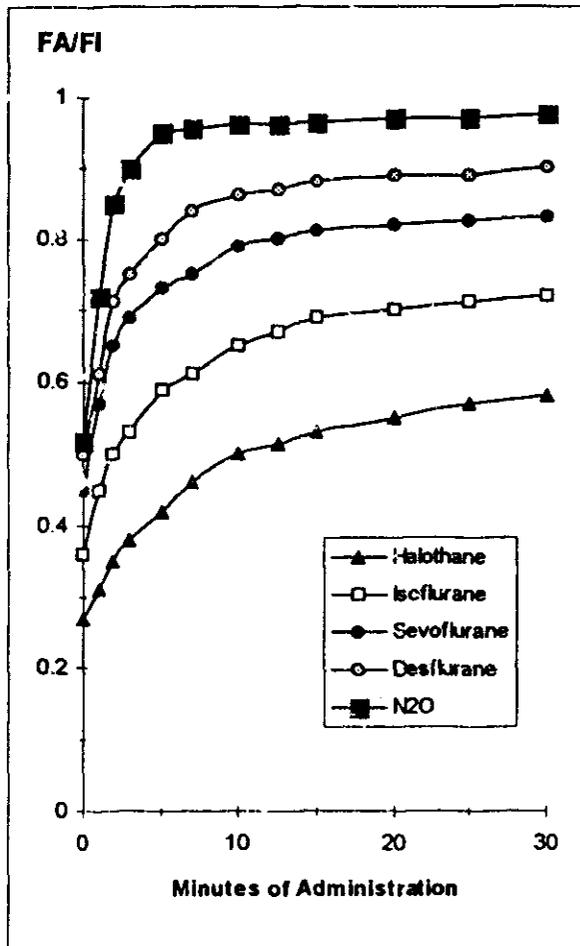
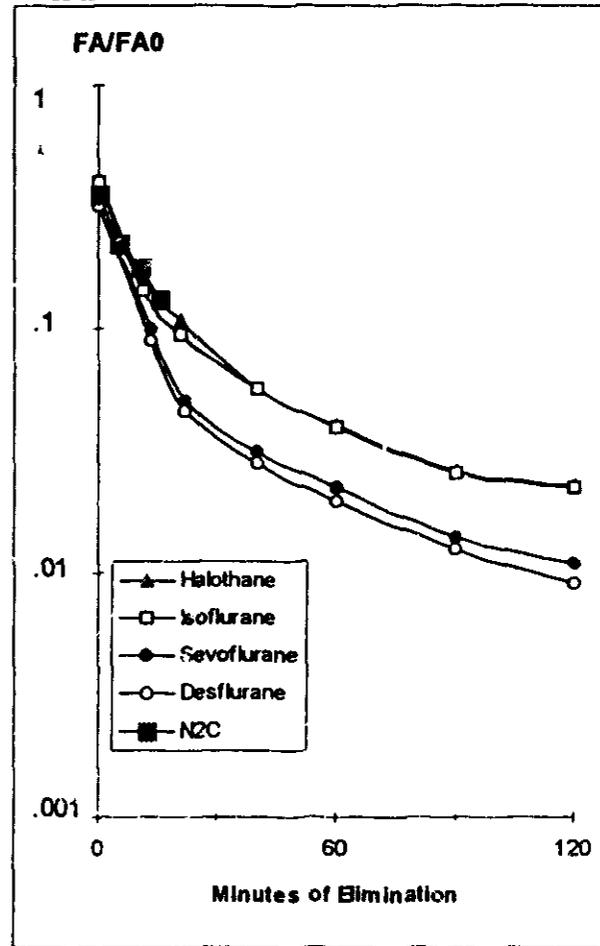


Figure 4. Concentration of anesthetic in alveolar gas following termination of anesthesia.



Yasuda N, Lockhart S, Eger EI II, et al: Comparison of kinetics of sevoflurane and isoflurane in humans. *Anesth Analg* 72:316, 1991.

#### Protein binding

The effects of sevoflurane on the displacement of drugs from serum and tissue proteins have not been investigated. Other fluorinated volatile anesthetics have been shown to displace drugs from serum and tissue proteins in vitro. The clinical significance of this is unknown. Clinical studies have shown no untoward effects when sevoflurane is administered to patients taking drugs that are highly bound and have a small volume of distribution (e.g., phenytoin).

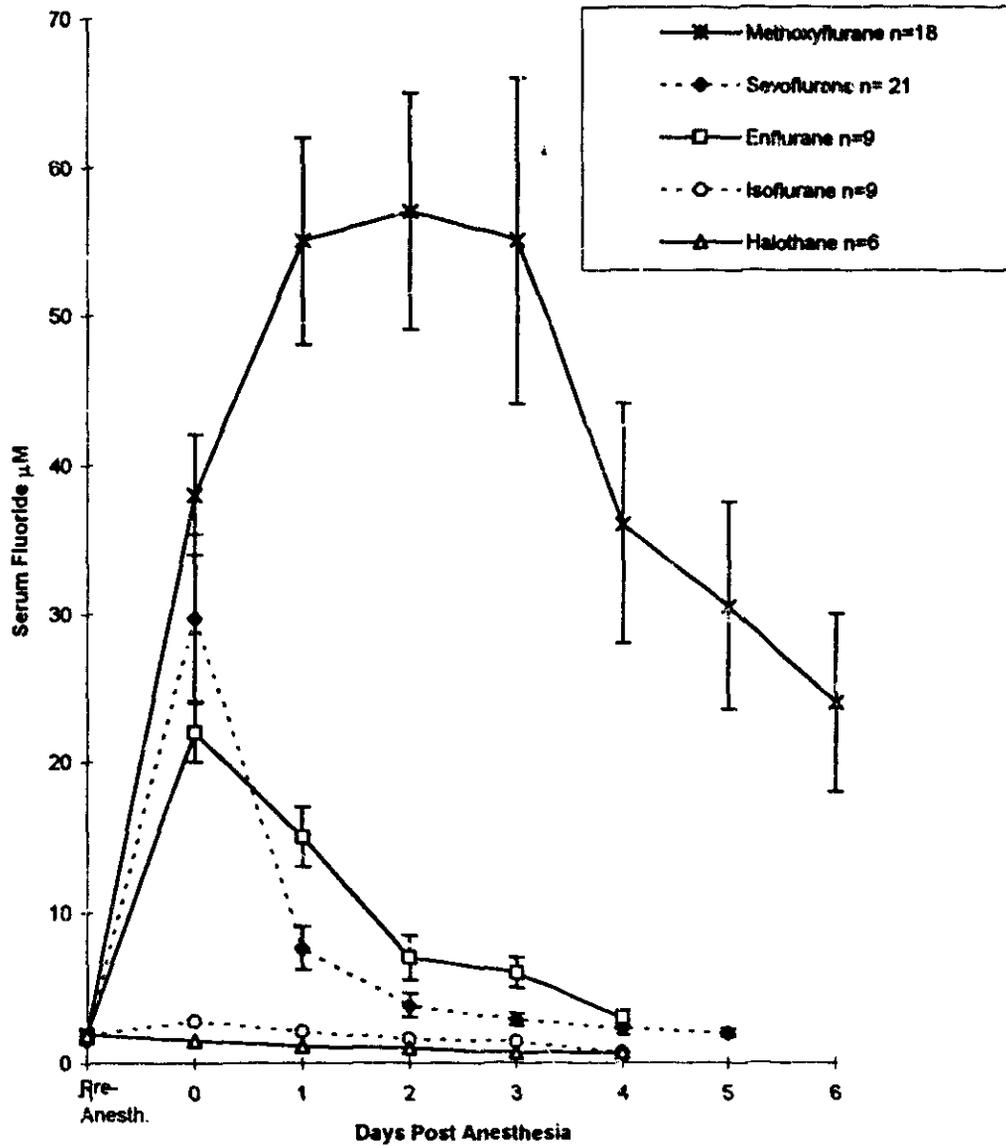
**Metabolism**

Sevoflurane is metabolized by cytochrome P450 2E1, to hexafluoroisopropanol (HFIP) with release of inorganic fluoride and CO<sub>2</sub>. Once formed, HFIP is rapidly conjugated with glucuronic acid and eliminated as a urinary metabolite. No other metabolic pathways for sevoflurane have been identified. In vivo metabolism studies suggest that approximately 5% of the sevoflurane dose may be metabolized.

Cytochrome P450 2E1 is the principal isoform identified for sevoflurane metabolism and this may be induced by chronic exposure to isoniazide and ethanol. This is similar to the metabolism of isoflurane and enflurane and is distinct from that of methoxyflurane which is metabolized via a variety of cytochrome P450 isoforms. The metabolism of sevoflurane is not inducible by barbiturates. As shown in Figure 5, inorganic fluoride concentrations peak within 2 hours of the end of sevoflurane anesthesia and return to baseline concentrations within 48 hours post-anesthesia in the majority of cases (67 %). The rapid and extensive pulmonary elimination of sevoflurane minimizes the amount of anesthetic available for metabolism.

Complete  
pg 49 4/16/95 label  
Complete  
pg 49 6/2/95 label

**Figure 5**  
**Serum inorganic fluoride concentrations for sevoflurane and other volatile anesthetics**



Cousins M.J., Greenstein L.R., Hitt B.A., et al: Metabolism and renal effects of enflurane in man. *Anesthesiology* 44:44; 1976 and Sevo-93-044.

Legend: Pre Anes. = Pre-anesthesia

*(Open up to)*  
*Clayton*  
*values differ as*  
*from this reference*

### Elimination

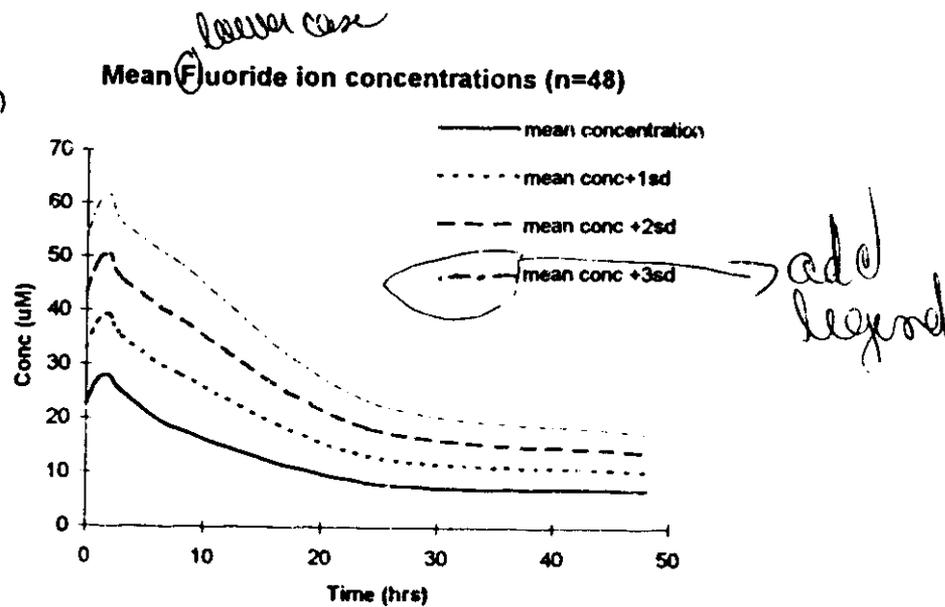
Up to 3.5% of the sevoflurane dose appears in the urine as inorganic fluoride. Studies on fluoride indicate that up to 50% of fluoride clearance is nonrenal (via fluoride being taken up into bone).

### Pharmacokinetics of fluoride ion

Fluoride ion concentrations are influenced by the duration of anesthesia, the concentration of sevoflurane administered, and the composition of the anesthetic gas mixture. In studies where anesthesia was maintained purely with sevoflurane for periods ranging from 1 to 6 hours, peak fluoride concentrations ranged between  $12\mu\text{M}$  and  $90\mu\text{M}$ . As shown in Figure 6, peak concentrations occur within 2 hours of the end of anesthesia and are less than  $25\mu\text{M}$  ( $475\text{ng/mL}$ ) for the majority of the population after 10 hours. The half life is in the range of 15-23 hours.

It has been reported that following administration of methoxyflurane, serum inorganic fluoride concentrations  $> 50\mu\text{M}$  were correlated with the development of vasopressin-resistant, polyuric, renal failure. In clinical trials with sevoflurane, there were no reports of toxicity associated with elevated fluoride ion levels.

Figure 6: Fluoride ion concentrations following administration of sevoflurane (mean MAC = 1.27, mean duration = 2.06 hr)



### Fluoride concentrations after repeat exposure and in special populations

Fluoride concentrations have been measured after single, extended, and repeat exposure to sevoflurane in normal surgical and special patient populations, and pharmacokinetic parameters were determined.

Compared with healthy individuals, the fluoride ion half-life was prolonged in patients with renal impairment, but not in the elderly. A study in 8 patients with hepatic impairment suggests a slight prolongation of the half-life. The mean half-life in patients with renal impairment averaged approximately 33 hours (range 21-61 hours) as compared to a mean of approximately 21 hours (range 10-48) in normal healthy individuals. The mean half-life in the elderly (> 65 years) approximated 24 hours (range 18-72 hours). The mean half-life in individuals with hepatic impairment was 23 hours (range 16-47 hours). Mean maximal fluoride values ( $C_{max}$ ) determined in individual studies of special populations are displayed below.

**Table 1. Fluoride ion estimates in special populations following administration of sevoflurane**

	n	Age (yr)	Duration of anesthesia (hr)	Dose (MAC-hr)	$C_{max}$ ( $\mu$ M)
<b>PEDIATRIC PATIENTS</b>					
<b>Anesthetic</b>					
Sevoflurane-O <sub>2</sub>	76	0-11	0.8	1.1	12.6
Sevoflurane-O <sub>2</sub>	40	1-11	2.2	3.0	16.0
Sevoflurane/N <sub>2</sub> O	25	5-13	1.9	2.4	21.3
Sevoflurane/N <sub>2</sub> O	42	0-18	2.4	2.2	18.4
Sevoflurane/N <sub>2</sub> O	40	1-11	2.0	2.6	15.5
<b>ELDERLY</b>	33	65-93	2.6	1.4	25.6
<b>RENAL</b>	21	29-83	2.5	1.0	26.1
<b>HEPATIC</b>	8	42-79	3.6	2.2	30.6
<b>OBESE</b>	35	24-73	3.0	1.7	38.0

n = number of patients studied

**Pharmacodynamics**

Changes in the depth of sevoflurane anesthesia rapidly follow changes in the inspired concentration. In the sevoflurane clinical program, the following recovery variables were evaluated:

1. Time to events measured from the end of study drug:
  - time to removal of the endotracheal tube (extubation time)
  - time required for the patient to open his/her eyes on verbal command (emergence time)
  - time to respond to simple command (e.g., "squeeze my hand") or demonstrates purposeful movement (response to command time, orientation time)
2. Recovery of cognitive function and motor coordination was evaluated based on:
  - psychomotor performance tests (Digit Symbol Substitution Test [DSST], Treiger Dot test)
  - the results of subjective (Visual Analog Scale [VAS]) and objective (objective pain-discomfort scale [OPDS]) measurements
  - time to administration of the first post-anesthesia analgesic medication
  - assessments of post-anesthesia patient status
3. Other recovery times were:
  - time to achieve an Aldrete Score of  $\geq 8$
  - time required for the patient to be eligible for discharge from the recovery area, per standard criteria at site
  - time when the patient was eligible for discharge from the hospital
  - time when the patient was able to sit-up or stand without dizziness

Some of these variables are summarized as follows:

**TABLE 2: INDUCTION AND RECOVERY VARIABLES FOR EVALUABLE PEDIATRIC PATIENTS IN TWO COMPARATIVE STUDIES**

<u>Time to End-Point (min)</u>	<u>Sevoflurane</u> Mean $\pm$ SEM 2.0 $\pm$ 0.2 (n=294)	<u>Halothane</u> Mean $\pm$ SEM 2.7 $\pm$ 0.2 (n=252)
Induction	11.3 $\pm$ 0.7 (n=293)	15.8 $\pm$ 0.8 (n=252)
Emergence	13.7 $\pm$ 1.0 (n=271)	19.3 $\pm$ 1.1 (n=230)
Response to Command	52.2 $\pm$ 8.5 (n=216)	67.6 $\pm$ 10.6 (n=150)
First Analgesia	76.5 $\pm$ 2.0 (n=292)	81.1 $\pm$ 1.9 (n=246)
Eligible for recovery discharge		

n = number of patients with recording of events

**TABLE 3: RECOVERY VARIABLES FOR EVALUABLE ADULT PATIENTS IN TWO COMPARATIVE STUDIES: SEVOFLURANE VERSUS ISOFLURANE**

<u>Time to parameter: (min)</u>	<u>Sevoflurane</u> Mean $\pm$ SEM (n=395)	<u>Isoflurane</u> Mean $\pm$ SEM (n=348)
Emergence	7.7 $\pm$ 0.3	9.1 $\pm$ 0.3
Response to command	8.1 $\pm$ 0.3 (n=395)	9.7 $\pm$ 0.3 (n=345)
First analgesia	42.7 $\pm$ 3.0 (n=269)	52.9 $\pm$ 4.2 (n=228)
Eligible for recovery discharge	87.6 $\pm$ 5.3 (n=244)	79.1 $\pm$ 5.2 (n=252)

n = number of patients with recording of recovery events. *delete*

**TABLE 4: META-ANALYSES OF INDUCTION AND EMERGENCE VARIABLES FOR EVALUABLE ADULT PATIENTS IN COMPARATIVE STUDIES: SEVOFLURANE VERSUS PROPOFOL**

<u>Parameter</u>	<u>No. of Studies</u>	<u>Sevoflurane</u> Mean $\pm$ SEM (n=259)	<u>Propofol</u> Mean $\pm$ SEM (n=258)
Mean maintenance anesthetic exposure $\pm$ SD	3	1.0 MAC-hr. $\pm$ 0.8	7.2 mg/kg/hr $\pm$ 2.6
Time to induction (min)	1	3.1 $\pm$ 0.18* (n=93)	2.2 $\pm$ 0.18** (n=93)
Time to emergence (min)	3	8.6 $\pm$ 0.57 (n=255)	11.0 $\pm$ 0.57 (n=260)
Time to response to command (min)	3	9.9 $\pm$ 0.60 (n=257)	12.1 $\pm$ 0.60 (n=260)
Time to first analgesia (min)	3	43.8 $\pm$ 3.79 (n=177)	57.9 $\pm$ 3.68 (n=179)
Time to eligibility for recovery discharge (min)	3	116.0 $\pm$ 4.15 (n=257)	115.6 $\pm$ 3.98 (n=261)

\*Propofol induction of one sevoflurane group = mean of 178.8mg  $\pm$  72.5 SD (n=165)

\*\*Propofol induction of all propofol groups = mean of 170.2mg  $\pm$  60.6 SD (n=245)

n = number of patients with recording of events

*Propofol added to make it easier to read*

*delete "..."*

Cardiovascular Effects

Sevoflurane was studied in 14 healthy volunteers (18-35 years old) comparing sevoflurane-O<sub>2</sub> (Sevo/O<sub>2</sub>) to sevoflurane-N<sub>2</sub>O/O<sub>2</sub> (Sevo/N<sub>2</sub>O/O<sub>2</sub>) during 7 hours of anesthesia. During controlled ventilation, parameters measured are shown in figures 7-10:

Figure 7: HEART RATE

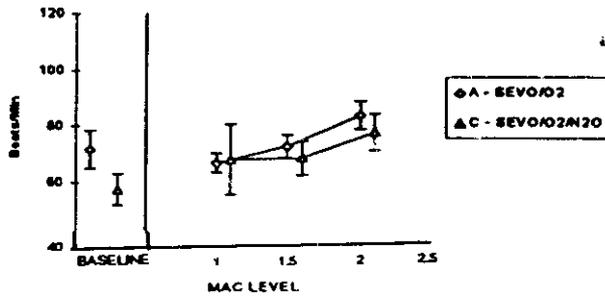


Figure 8: MEAN ARTERIAL PRESSURE

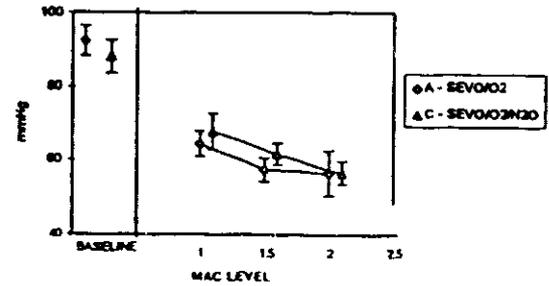


Figure 9: SYSTEMIC VASCULAR RESISTANCE

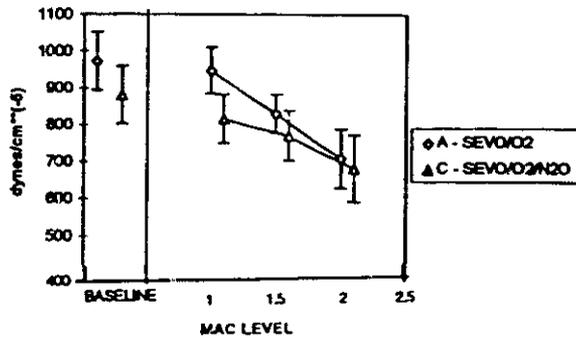
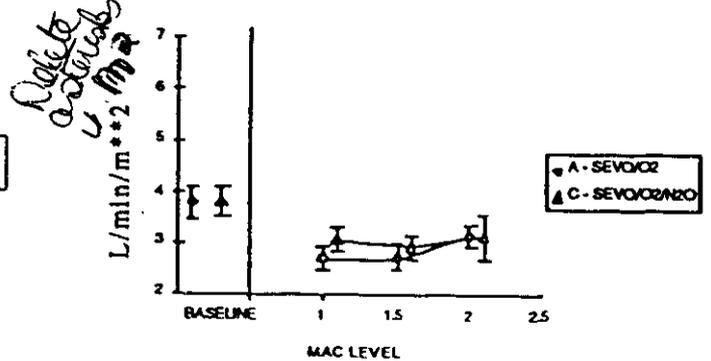


Figure 10: CARDIAC INDEX



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*Delete asterisks L/min/m<sup>2</sup>*

*CCP 10/11 Hypotension 9/07*

Sevoflurane is a dose-related cardiac depressant. Sevoflurane does not produce increases in heart rate at doses less than 2 MAC.

A study investigating the epinephrine induced arrhythmogenic effect of sevoflurane versus isoflurane in adult patients undergoing transsphenoidal hypophysectomy demonstrated that the threshold dose of epinephrine (i.e., the dose at which the first sign of arrhythmia was observed) producing multiple ventricular arrhythmias was 5 mcg/kg with both sevoflurane and isoflurane. Consequently, the interaction of sevoflurane with epinephrine appears to be equal to that seen with isoflurane.

## Clinical Trials

Sevoflurane was administered to a total of 3185 patients. The types of patients are summarized as follows:

**TABLE 5: PATENTS RECEIVING SEVOFLURANE IN CLINICAL TRIALS**

<u>TYPE OF PATIENTS</u>	<u>NUMBER STUDIED</u>
Adult	2223
Cesarean Delivery	29
Cardiovascular and patients at risk of myocardial ischemia	246
Neurosurgical	22
Hepatic impairment	8
Renal impairment	35
Pediatric	962

Clinical experience with these patients is described below.

### Adult Anesthesia

The efficacy of sevoflurane in comparison to isoflurane, enflurane, and propofol was investigated in 3 outpatient and 25 inpatient studies involving 3591 adult patients. Sevoflurane was found to be comparable to isoflurane, enflurane, and propofol for the maintenance of anesthesia in adult patients. Patients administered sevoflurane showed shorter times (statistically significant) to some recovery events (extubation, response to command, and orientation) than patients who received isoflurane or propofol.

### Mask Induction

Sevoflurane has a non-pungent odor and does not cause respiratory irritability. Sevoflurane is suitable for mask induction in adults. In 196 patients, mask induction was smooth and rapid with complications occurring with the following frequencies: cough, 6%; breathholding, 6%; agitation, 6%; laryngospasm, 5%.

### Ambulatory Surgery

Sevoflurane was compared to isoflurane and propofol for maintenance of anesthesia supplemented with N<sub>2</sub>O in two studies involving 786 adult (18-84 years of age) ASA Class I, II, or III patients. Shorter times to emergence and response to commands (statistically significant) were observed with sevoflurane compared to isoflurane and propofol.

**TABLE 6: RECOVERY PARAMETERS IN TWO OUTPATIENT SURGERY STUDIES:  
LEAST SQUARES MEAN ± SEM**

	<u>Sevoflurane/N<sub>2</sub>O</u>	<u>Isoflurane/N<sub>2</sub>O</u>	<u>Sevoflurane/ N<sub>2</sub>O</u>	<u>Propofol/ N<sub>2</sub>O</u>
Mean maintenance anesthesia exposure±SD	0.64 ± 0.03 MAC-hr (n=245)	0.66 ± 0.03 MAC-hr (n=249)	0.8 ± 0.5 MAC-hr (n=166)	7.3 ± 2.3 mg/kg/hr (n=166)
Time to emergence (min)	8.2 ± 0.4 (n = 246)	9.3±0.3 (n=251)	8.3 ± 0.7 (n=137)	10.4 ± 0.7 (n=142)
Time to response to commands (min)	8.5± 0.4 (n=246)	9.8± 0.4 (n=248)	9.1 ± 0.7 (n=139)	11.5 ± 0.7 (n=143)
Time to first analgesia (min)	45.9± 4.7 (n=160)	59.1± 6.0 (n=252)	46.1± 5.4 (n=83)	60.0 ± 4.7 (n=88)
Time to eligibility for discharge from recovery area (min)	87.6± 5.3 (n=244)	79.1± 5.2 (n=252)	103.1 ± 3.8 (n=139)	105.1 ± 3.7 (n=143)

n = number of patients with recording of recovery events

### Inpatient Surgery

Sevoflurane was compared to isoflurane and propofol for maintenance of anesthesia supplemented with N<sub>2</sub>O in two multicenter studies involving 741 adult ASA Class I, II, or III (18-92 years of age) patients. Shorter times to emergence, command response, and first post-anesthesia analgesia (statistically significant) were observed with sevoflurane compared to isoflurane and propofol.

**TABLE 7: RECOVERY PARAMETERS IN TWO INPATIENT SURGERY STUDIES:  
LEAST SQUARES MEAN ± SEM**

	<u>Sevoflurane/N<sub>2</sub>O</u>	<u>Isoflurane/ N<sub>2</sub>O</u>	<u>Sevoflurane/ N<sub>2</sub>O</u>	<u>Propofol/ N<sub>2</sub>O</u>
Mean maintenance anesthetic exposure +SD	1.27 MAC-hr ± 0.05 (n=271)	1.58 MAC-hr ± 0.06 (n=282)	1.43 MAC-hr ± 0.94 (n=93)	7.0 mg/kg/hr ± 2.9 (n=92)
Time to emergence (min)	11.0 ± 0.6 (n=270)	16.4 ± 0.6 (n=281)	8.2 ± 1.2 (n=92)	13.2 ± 1.2 (n=92)
Time to respond to commands (min)	12.8 ± 0.7 (n=270)	18.4 ± 0.7 (n=281)	11.0 ± 1.20 (n=92)	14.4 ± 1.21 (n=91)
Time to first analgesia (min)	46.1 ± 3.0 (n=233)	55.4 ± 3.2 (n=242)	37.8 ± 3.3 (n=82)	49.2 ± 3.3 (n=79)
Time to eligibility for discharge from recovery area (min)	139.2 ± 15.6 (n=268)	165.9 ± 16.3 (n=282)	148.4 ± 8.9 (n=92)	141.4 ± 8.9 (n=92)

n = number of patients with recording of recovery events

### **Pediatric Anesthesia**

The concentration of sevoflurane required for maintenance of general anesthesia is age-dependent (see DOSAGE AND ADMINISTRATION). Sevoflurane or halothane was used to anesthetize 1588 pediatric patients aged 1 day to 18 years, and ASA physical status I or II (927 sevoflurane, 661 halothane). In one study involving 90 infants and children, there were no clinically significant decreases in heart rate compared to awake values at 1 MAC. Systolic blood pressure decreased 15-20% in comparison to awake values following administration of 1 MAC sevoflurane; however, clinically significant hypotension requiring immediate intervention did not occur. Overall incidences of bradycardia [more than 20 beats/min lower than normal (80 beats/min)] in comparative studies were 3% for sevoflurane and 7% for halothane. Patients who received sevoflurane had slightly faster emergence times (12 vs 19 minutes), and a higher incidence of post-anesthesia agitation (14% vs 10%).

### **Mask Induction**

Sevoflurane has a non-pungent odor and is suitable for mask induction in children. In controlled pediatric studies in which mask induction was performed, the incidence of induction events is shown below (See ADVERSE REACTIONS: Possibly/Probably Causally Related):

**Table 8: Incidence of Pediatric Induction Events**

	<u>Sevoflurane</u> (n=836)	<u>Halothane</u> (n=660)
Agitation	14%	11%
Cough	6%	10%
Breath holding	5%	6%
Secretions	3%	3%
Laryngospasm	2%	2%
Bronchospasm	<1%	0%

n = number of patients

### **Ambulatory Surgery**

Sevoflurane (n=518) was compared to halothane (n=382) for the maintenance of anesthesia in pediatric outpatients. All patients received N<sub>2</sub>O and many received fentanyl, midazolam, bupivacaine, or lidocaine. The time to eligibility for discharge from post-anesthesia care units was similar between agents (see CLINICAL PHARMACOLOGY and ADVERSE REACTIONS).

## **Cardiovascular Surgery**

### **Coronary Artery Bypass Graft (CABG) Surgery**

Sevoflurane was compared to isoflurane as an adjunct with opioids in a multicenter study of 273 patients undergoing CABG surgery. Anesthesia was induced with midazolam (0.1 - 0.3 mg/kg), vecuronium (0.1 - 0.2 mg/kg), and fentanyl (5 - 15 mcg/kg). Both isoflurane and sevoflurane were administered at loss of consciousness in doses of 1.0 MAC and titrated until the beginning of cardiopulmonary bypass to a maximum of 2.0 MAC. The total dose of fentanyl did not exceed 25 mcg/kg. The average MAC dose was 0.49 for sevoflurane and 0.53 for isoflurane. There were no significant differences in hemodynamics, cardioactive drug use, or ischemia incidence between the two groups. Outcome was also equivalent. In this small multicenter study, sevoflurane appears to be as effective and as safe as isoflurane for supplementation of opioid anesthesia for coronary bypass grafting.

### **Non-Cardiac Surgery Patients at Risk for Myocardial Ischemia**

Sevoflurane-N<sub>2</sub>O was compared to isoflurane-N<sub>2</sub>O for maintenance of anesthesia in a multicenter study in 214 patients, age 40-87 years who were at mild-to-moderate risk for myocardial ischemia and were undergoing elective non-cardiac surgery. Forty-six percent (46%) of the operations were cardiovascular, with the remainder evenly divided between gastrointestinal and musculoskeletal and small numbers of other surgical procedures. The average duration of surgery was less than 2 hours. Anesthesia induction usually was performed with thiopental (2-5 mg/kg) and fentanyl (1-5 mcg/kg). Vecuronium (0.1-0.2 mg/kg) was also administered to facilitate intubation, muscle relaxation, or immobility during surgery. The average MAC dose was 0.49 for both anesthetics. There was no significant difference between the anesthetic regimens for intraoperative hemodynamics, cardioactive drug use, or ischemic incidents, although only 83 patients in the sevoflurane group and 85 patients in the isoflurane group were successfully monitored for ischemia. The outcome was also equivalent in terms of adverse events, death, and postoperative myocardial infarction. Within the limits of this small multicenter study in patients at mild-to-moderate risk for myocardial ischemia, sevoflurane was a satisfactory equivalent to isoflurane in providing supplemental inhalation anesthesia to intravenous drugs.

## **Cesarean Section**

Sevoflurane (n=29) was compared to isoflurane (n=27) in ASA Class I or II patients for the maintenance of anesthesia during cesarean section. Newborn evaluations and recovery events were recorded. With both anesthetics, Apgar scores averaged 8 and 9 at 1 and 5 minutes respectively.

Use of sevoflurane as part of general anesthesia for elective cesarean section produced no untoward effects in mother or neonate. Sevoflurane and isoflurane demonstrated equivalent recovery characteristics. There was no difference between sevoflurane and isoflurane with regard to the effect on the newborn, as assessed by Apgar Score and Neurological and Adaptive Capacity Score (average=29.5). The safety of sevoflurane in labor and vaginal delivery has not been evaluated.

## **Neurosurgery**

Three studies compared sevoflurane to isoflurane for maintenance of anesthesia during neurosurgical procedures. In a study of 20 patients, there was no difference between sevoflurane and isoflurane with regard to recovery from anesthesia. In 2 studies, a total of 22 patients with intracranial pressure (ICP) monitors received either sevoflurane or isoflurane. There was no difference between sevoflurane and isoflurane with regard to ICP response to inhalation of 0.5, 1.0, and 1.5 MAC inspired concentrations of volatile agent during N<sub>2</sub>O-O<sub>2</sub>-fentanyl anesthesia. During progressive hyperventilation from PaCO<sub>2</sub> = 40 to PaCO<sub>2</sub> = 30, ICP response to hypocarbia was preserved with sevoflurane at both 0.5 and 1.0 MAC concentrations. In patients at risk for elevations of ICP, sevoflurane should be administered cautiously in conjunction with ICP-reducing maneuvers such as hyperventilation.

### **Hepatic Impairment**

A multicenter study (2 sites) compared the safety of sevoflurane and isoflurane in 16 patients with mild-to-moderate hepatic impairment utilizing the lidocaine MEGX assay for assessment of hepatocellular function. All patients received intravenous propofol (1-3 mg/kg) or thiopental (2-7 mg/kg) for induction and succinylcholine, vecuronium, or atracurium for intubation. Sevoflurane or isoflurane was administered in either 100% O<sub>2</sub> or up to 70% N<sub>2</sub>O/O<sub>2</sub>. Neither drug adversely affected hepatic function. No serum inorganic fluoride level exceeded 45 μM/L, but sevoflurane patients had prolonged terminal disposition of fluoride, as evidenced by longer inorganic fluoride half-life than patients with normal hepatic function (23 hours vs 10-18 hours).

### **Renal Impairment**

Sevoflurane was evaluated in renally impaired patients with baseline serum creatinine >1.5 mg/dL. Fourteen patients who received sevoflurane were compared with 12 patients who received isoflurane. In another study, 21 patients who received sevoflurane were compared with 20 patients who received enflurane. Creatinine levels increased in 7% of patients who received sevoflurane, 8% of patients who received isoflurane, and 10% of patients who received enflurane. Because of the small number of patients with renal insufficiency (baseline serum creatinine greater than 1.5 mg/dL) studied, the safety of sevoflurane administration in this group has not yet been fully established. Therefore, sevoflurane should be used with caution in patients with renal insufficiency.

## **INDICATIONS AND USAGE**

Sevoflurane is indicated for induction and maintenance of general anesthesia in adult and pediatric patients for inpatient and outpatient surgery.

## **CONTRAINDICATIONS**

Sevoflurane can cause malignant hyperthermia; it should not be used in patients with known history of sensitivity to sevoflurane or to other halogenated agents.

## **WARNINGS**

Sevoflurane should be administered only by persons trained in the administration of general anesthesia. Facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment, and circulatory resuscitation must be immediately available. Since levels of anesthesia may be altered rapidly, only vaporizers producing predictable concentrations of sevoflurane should be used.

Compound A is produced when sevoflurane interacts with soda lime and Baralyme® (See DESCRIPTION). Its concentration in a circle absorber system increases with increasing absorber temperature and increasing sevoflurane concentrations and with decreasing fresh gas flow rates. Although Compound A is a dose-dependent nephrotoxin in rats, the mechanism of this renal toxicity is unknown and has not been established in humans. Because of limited clinical experience with sevoflurane in low-flow systems, fresh gas flow rates below 2 L/min in a circle absorber system are not recommended.

Because clinical experience in administering sevoflurane to patients with renal insufficiency (creatinine >1.5 mg/dL) is limited, its safety in these patients has not been established.

### **Malignant Hyperthermia**

In susceptible individuals, potent inhalation anesthetic agents, including sevoflurane, may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. In clinical trials, one case of malignant hyperthermia was reported. In genetically susceptible pigs, sevoflurane induced malignant hyperthermia. The clinical syndrome is signaled by hypercapnia, and may include muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and/or unstable blood pressure. Some of these nonspecific signs may also appear during light anesthesia, acute hypoxia, hypercapnia, and hypovolemia.

Treatment of malignant hyperthermia includes discontinuation of triggering agents, administration of intravenous dantrolene sodium, and application of supportive therapy. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be monitored and sustained if possible.

Sevoflurane may present an increased risk in patients with known sensitivity to volatile halogenated anesthetic agents.

### **PRECAUTIONS**

During the maintenance of anesthesia, increasing the concentration of sevoflurane produces dose-dependent decreases in blood pressure. Due to sevoflurane's insolubility in blood, these hemodynamic changes may occur more rapidly than with other volatile anesthetics. Excessive decreases in blood pressure or respiratory depression may be related to depth of anesthesia and may be corrected by decreasing the inspired concentration of sevoflurane.

The recovery from general anesthesia should be assessed carefully before patient is discharged from the post-anesthesia care unit.

### **Drug Interactions**

In clinical trials, no significant adverse reactions occurred with other drugs commonly used in the perioperative period, including: central nervous system depressants, autonomic drugs, skeletal muscle relaxants, anti-infective agents, hormones and synthetic substitutes, blood derivatives, and cardiovascular drugs.

#### *Intravenous anesthetics:*

Sevoflurane administration is compatible with barbiturates, propofol, and other commonly used intravenous anesthetics.

#### *Benzodiazepines and Opioids:*

Benzodiazepines and opioids would be expected to decrease the MAC of sevoflurane in the same manner as with other inhalational anesthetics. Sevoflurane administration is compatible with benzodiazepines and opioids as commonly used in surgical practice.

#### *Nitrous oxide:*

As with other halogenated volatile anesthetics, the anesthetic requirement for sevoflurane is decreased when administered in combination with nitrous oxide. Using 50% N<sub>2</sub>O, the MAC equivalent dose requirement is reduced approximately 50% in adults, and approximately 25% in pediatric patients. (See DOSAGE AND ADMINISTRATION)

### Neuromuscular Blocking Agents:

As is the case with other volatile anesthetics, sevoflurane increases both the intensity and duration of neuromuscular blockade induced by non-depolarizing muscle relaxants. When used to supplement alfentanil-N<sub>2</sub>O anesthesia, sevoflurane and isoflurane equally potentiate neuromuscular block induced with pancuronium, vecuronium or atracurium. Therefore, during sevoflurane anesthesia, the dosage adjustments for these muscle relaxants are similar to those required with isoflurane.

Potential of neuromuscular blocking agents requires equilibration of muscle with delivered partial pressure of sevoflurane. Reduced doses of neuromuscular blocking agents during induction of anesthesia may result in delayed onset of conditions suitable for endotracheal intubation or inadequate muscle relaxation.

Among available nondepolarizing agents, only vecuronium, pancuronium, and atracurium interactions have been studied during sevoflurane anesthesia. In the absence of specific guidelines:

1. For endotracheal intubation, do not reduce the dose of nondepolarizing muscle relaxants.
2. During maintenance of anesthesia, the required dose of nondepolarizing muscle relaxants is likely to be reduced compared to that during N<sub>2</sub>O/opioid anesthesia. Administration of supplemental doses of muscle relaxants should be guided by the response to nerve stimulation.

The effect of sevoflurane on the duration of depolarizing neuromuscular blockade induced by succinylcholine has not been studied.

### **Renal or Hepatic Function**

Results of evaluations of laboratory parameters (e.g., ALT, AST, alkaline phosphatase, and total bilirubin, etc.), as well as investigator-reported incidence of adverse events relating to liver function, demonstrate that sevoflurane can be administered to patients with normal or mild-to-moderately impaired hepatic function. However, patients with severe hepatic dysfunction were not investigated.

Occasional cases of transient changes in postoperative hepatic function tests were reported with both sevoflurane and reference agents. Sevoflurane was found to be comparable to isoflurane with regard to these changes in hepatic function.

Based on the incidence and magnitude of changes in serum creatinine, in patients with exposure up to 9.6 MAC-hours of sevoflurane anesthesia, no evidence for increased risk of developing renal dysfunction was found.

Serum fluoride levels increased with duration and concentration of exposure to sevoflurane. The highest measured serum fluoride level was 111 µM and a level of 29.5 µM was seen as late as 92 hours post exposure. A 25% reduction in maximum urine-concentrating ability has been seen following enflurane anesthesia with mean peak serum inorganic fluoride levels of 33.6 µM and values above 20 µM for 18 hours. Elevated fluoride levels after sevoflurane were not associated with impairment of renal function, presumably because of its rapid elimination at the end of anesthesia.

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Studies on carcinogenesis have not been performed. No mutagenic effect was noted in the Ames test and no chromosomal aberrations were induced in cultured mammalian cells.

**Pregnancy Category B**

Reproduction studies have been performed in rats and rabbits at doses up to 1 MAC (minimum alveolar concentration) without CO<sub>2</sub> absorbent and have revealed no evidence of impaired fertility or harm to the fetus due to sevoflurane at 0.3 MAC, the highest nontoxic dose. Developmental and reproductive toxicity studies of sevoflurane in animals in the presence of strong alkalis (i.e., degradation of sevoflurane and production of Compound A) have not been conducted. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, sevoflurane should be used during pregnancy only if clearly needed.

**Labor and Delivery** Sevoflurane has been used as part of general anesthesia for elective cesarean section in 29 women. There were no untoward effects in mother or neonate. (See CLINICAL PHARMACOLOGY, Clinical Trials) The safety of sevoflurane in labor and delivery has not been demonstrated.

**Nursing Mothers** The concentrations of sevoflurane in milk are probably of no clinical importance 24 hours after anesthesia. Because of rapid washout, sevoflurane concentrations in milk are predicted to be below those found with many other volatile anesthetics.

**Geriatric Use**

MAC decreases with increasing age. The average concentration of sevoflurane to achieve MAC in an 80 year old is approximately 50% of that required in a 20 year old.

**ADVERSE REACTIONS**

Adverse events are derived from controlled clinical trials conducted in the United States, Canada, and Europe. The reference drugs were isoflurane, enflurane, and propofol in adults and halothane in pediatric patients. The studies were conducted using a variety of premedications, other anesthetics, and surgical procedures of varying length. Most adverse events reported were mild and transient, and may reflect the surgical procedures, patient characteristics (including disease) and/or medications administered.

Of the 5182 patients enrolled in the clinical trials, 2906 were exposed to sevoflurane, including 118 adults and 507 pediatric patients who underwent mask induction. Each patient was counted once for each type of adverse event. Adverse events reported in patients in clinical trials and considered to be possibly or probably related to sevoflurane are presented within each body system in order of decreasing frequency in the following listings. One case of malignant hyperthermia was reported in pre-registration clinical trials.

**Adverse Events During the Induction Period (from onset of anesthesia by mask induction to surgical incision) Incidence >1%**

**Adult patients (N=118)**

*Cardiovascular*: Bradycardia 1%, Hypotension 4%, Tachycardia 2%

*Nervous System*:

*Respiratory System*: Laryngospasm 8%, Airway obstruction 8%, Breathholding 5%, Cough Increased 5%

**Pediatric Patients (N=507)**

*Cardiovascular*: Tachycardia 6%, Hypotension 4%

*Nervous System*: Agitation 15%

*Respiratory System*: Breathholding 5%, Cough Increased 5%, Laryngospasm 3%, Apnea 2%

*Digestive System*: Increased salivation 2%

**Adverse Events During Maintenance and Emergence Periods, Incidence >1% ( N = 2906)**

*Body as a whole*: Fever 1%, Shivering 6%, Hypothermia 1%, Movement 1%, Headache 1%

*Cardiovascular*: Hypotension 11%, Hypertension 2%, Bradycardia 5%, Tachycardia 2%

*Nervous System*: Somnolence 9%, Agitation 9%, Dizziness 4%, Increased salivation 4%

*Digestive*: Nausea 25%, Vomiting 18%

*Respiratory*: Cough increased 11%, Breathholding 2%, Laryngospasm 2%

**Adverse Events, All Patients in Clinical Trials (N = 2906), All Anesthetic Periods, Incidence < 1% (reported in 3 or more patients)**

*Body as a whole*: Asthenia, Pain

*Cardiovascular*: Arrhythmia, Ventricular Extrasystoles, Supraventricular Extrasystoles, Complete AV Block, Bigeminy, Hemorrhage, Inverted T Wave, Atrial Fibrillation, Atrial Arrhythmia, Second Degree AV Block, Syncope, S-T Depressed.

*Nervous System*: Crying, Nervousness, Confusion, Hypertonia, Dry Mouth, Insomnia

*Respiratory*: Sputum Increased, Apnea, Hypoxia, Wheezing, Bronchospasm, Hyperventilation, Pharyngitis, Hiccup, Hypoventilation, Dyspnea, Stridor

*Metabolism and Nutrition*: Increases in LDH, AST, ALT, BUN, Alkaline Phosphatase, Creatinine, Bilirubinemia, Glycosuria, Fluorosis, Albuminuria, Hypophosphatemia, Acidosis, Hyperglycemia

*Hemic and Lymphatic System*: Leucocytosis, Thrombocytopenia

*Skin and Special Senses*: Amblyopia, Pruritus, Taste Perversion, Rash, Conjunctivitis

*Urogenital*: Urination Impaired, Urine Abnormality, Urinary Retention, Oliguria

See WARNINGS for information regarding malignant hyperthermia.

## Laboratory Findings

Transient elevations in glucose, liver function tests, and white blood cell count may occur as with use of other anesthetic agents.

## OVERDOSAGE

In the event of overdosage, or what may appear to be overdosage, the following action should be taken: discontinue administration of sevoflurane, maintain a patent airway, initiate assisted or controlled ventilation with oxygen, and maintain adequate cardiovascular function.

## DOSAGE AND ADMINISTRATION

The concentration of sevoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using a vaporizer calibrated specifically for sevoflurane. The administration of general anesthesia must be individualized based on the patient's response.

**Pre-anesthetic medication:** No specific premedication is either indicated or contraindicated with sevoflurane. The decision as to whether or not to premedicate and the choice of premedication is left to the discretion of the anesthesiologist.

**Induction:** Sevoflurane has a non-pungent odor and does not cause respiratory irritability; it is suitable for mask induction in pediatrics and adults.

**Maintenance:** Surgical levels of anesthesia can usually be achieved with concentrations of 0.5 - 3% sevoflurane with or without the concomitant use of nitrous oxide. Sevoflurane can be administered with any type of anesthesia circuit.

Age of Patient (years)	Sevoflurane in Oxygen	Sevoflurane in 65% N <sub>2</sub> O/35% O <sub>2</sub>
0* - 1 months	3.3%	
1 - < 6 months	3.0%	
6 months - <3 years	2.8%	
3 - 12	2.5%	2.0% <sup>@</sup>
25	2.6%	1.4%
40	2.1%	1.1%
60	1.7%	0.9%
80	1.4%	0.7%

# Neonates are full-term gestational age. MAC in premature infants has not been determined.

@ In 3-<5 year old pediatric patients, 60% N<sub>2</sub>O/40% O<sub>2</sub> was used.

## HOW SUPPLIED

ULTANE™ (sevoflurane), Volatile Liquid for Inhalation, is packaged in amber colored bottles containing 250 mL sevoflurane, List 4456, NDC # 0074-4456-02.

## **SAFETY AND HANDLING**

**Occupational Caution:** *delete*

There is no specific work exposure limit established for sevoflurane. However, the National Institute for Occupational Safety and Health has recommended an 8 hour time-weighted average limit of 2 ppm for halogenated anesthetic agents in general (0.5 ppm when coupled with exposure to N<sub>2</sub>O).

## **STORAGE**

Store at controlled room temperature, 15° - 30°C (59° - 86°F).

Caution: Federal (USA) law prohibits dispensing without prescription.

Manufactured by:

ABBOTT LABORATORIES, North Chicago, IL 60064, USA under license from Maruishi Pharmaceutical Company LTD. 2-3-5, Fushimi-machi, Chuo-Ku, Osaka, Japan.

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# COPY

EXCLUSIVITY SUMMARY FOR NDA # 20-478 SUPPL # \_\_\_\_\_

Trade Name Ultane (sevoflurane) Generic Name sevoflurane  
Applicant Name Abbott HFD # 007  
Approval Date If Known 9/7/95

## PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

- a) Is it an original NDA? YES /  / NO /  /
- b) Is it an effectiveness supplement? YES /  / NO /  /

If yes, what type? (SE1, SE2, etc.) \_\_\_\_\_

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /  / NO /  /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

↓  
\_\_\_\_\_  
\_\_\_\_\_

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

↓  
\_\_\_\_\_  
\_\_\_\_\_

d). Did the applicant request exclusivity?

YES /  / NO /  /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES /  / NO /  /

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /  / NO /  /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

### 1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /  / NO /  /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# \_\_\_\_\_  
NDA# \_\_\_\_\_  
NDA# \_\_\_\_\_

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /\_\_\_/ <sup>N/A</sup> NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# \_\_\_\_\_  
NDA# \_\_\_\_\_  
NDA# \_\_\_\_\_

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /  / NO /  /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /  / NO /  /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /  / NO /  /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion?

YES /\_\_\_/ NO /\_\_\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO /\_\_\_/ ✓

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

\_\_\_\_\_  
\_\_\_\_\_

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

YES /\_\_\_/

NO //

Investigation #2

YES /\_\_\_/

NO //

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

YES /\_\_\_/

NO //

Investigation #2

YES /\_\_\_/

NO //

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Sevo 92-003

Sevo 92-010

Sevo 92-001

\_\_\_\_\_

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

	Investigation #1	!	
IND #	YES / <input checked="" type="checkbox"/> /	!	NO / ___ / Explain: _____
		!	_____
	Investigation #2	!	
IND #	YES / <input checked="" type="checkbox"/> /	!	NO / ___ / Explain: _____
		!	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

	Investigation #1	!	
	YES / ___ / Explain _____	!	NO / ___ / Explain _____
	_____	!	_____
	_____	!	_____
	Investigation #2	!	
	YES / ___ / Explain _____	!	NO / ___ / Explain _____
	_____	!	_____
	_____	!	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  / NO

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

*Luigi Vaccari*  
Signature  
Title: CSO

3-20-95  
Date

*Robert F. Bedford*  
Signature of Office/  
Division Director

6/7/95  
Date

cc: Original NDA      Division File      HFD-85 Mary Ann Ward  
    20-478

DRUG STUDIES IN PEDIATRIC PATIENTS  
(To be completed for all NME's recommended for approval)

NDA # 20-478

Trade (generic) names Ultara (sevoflurane)

Check any of the following that apply and explain, as necessary, on the next page:

Yes

1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

No

2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&MC studies in children.

a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

N/A

3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

a. The applicant has committed to doing such studies as will be required.

- (1) Studies are ongoing.  
 (2) Protocols have been submitted and approved.  
 (3) Protocols have been submitted and are under review.  
 (4) If no protocol has been submitted, on the next page explain the status of discussions.

b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

N/A

4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.



VACCARI

March 22, 1995

**DIVISION DIRECTOR'S OVERVIEW OF CLINICAL STUDY REVIEWS  
AND NDA-DAY SUMMARY  
PILOT DRUG EVALUATION STAFF**

**NDA #:** 20-478

**MAR 22 1995**

**Drug:** Sevoflurane (Sevorane):

**Sponsor:** Abbott Laboratories  
Abbott Park, IL 60064

**Reviewer:** Robert F. Bedford, M.D., Medical Officer.

**NDA submitted:** July 11, 1994

**Advisory Committee Meeting Date:** Jan 17-18, 1995

**CSO:** Leslie Vaccari

**Resume and Background**

This NDA is for a new inhalational general anesthetic. It has been in use of Japan since 1990, with several million patient exposures. Its efficacy is not in doubt. Unlike other volatile anesthetics, it is not unpleasant to inhale. Due to its low solubility in blood and fat, it is characterized by rapid onset and termination of action. Toxicity reports from Japan suggest that its safety profile is virtually identical to other halogenated inhalational anesthetics.

The most controversial aspect of this drug pertains to a breakdown product, (Compound A) produced by the interaction of sevoflurane with the carbon dioxide absorbents used in rebreathing anesthesia systems. Compound A is nephrotoxic to rats, with an LD50 of approximately 200 ppm after 6 hours of exposure and a minimal toxic concentration of 50-100 ppm. Early commercial development of sevoflurane was delayed due to recognition of this toxicity, (see Dr. Terrell's correspondence in attached appendix). An additional source of potential nephrotoxicity is due to hepatic metabolism of sevoflurane by cytochrome P450-2E1. This pathway releases free fluoride, a known nephrotoxin correlated with nephrogenic diabetes insipidus following exposure to methoxyflurane anesthesia. Safety concerns regarding sevoflurane, then, relate to the possibility that patients might be exposed to two nephrotoxins, particularly if they have been exposed to enzyme-inducing drugs such as isoniazide.

**Clinical Studies:**

The sponsor submitted 40 clinical studies to the NDA. Sevoflurane was used as the primary anesthetic in over 3000 patients, including children less than a year of age. The agent was found to be rapid-acting and easily controlled in a wide variety of surgical procedures. Patients usually emerged from anesthesia faster from sevoflurane than from comparator inhalational agents. This was not unexpected, however, because: 1) the comparator agents were more soluble anesthetics and 2) higher dose-equivalents of comparator agents tended to be administered in the trials.

Almost all submitted studies used relatively high fresh gas flows, thus bypassing the carbon dioxide absorber and resulting in low levels of Compound A, when it was measured. Since Japanese clinicians also tend to use high-flow anesthesia, the overall human experience with Compound A exposure is limited at this time and the Japanese database is somewhat suspect regarding the possible occurrence of postanesthetic renal dysfunction.

**Serious Adverse Events:**

One cases of malignant hyperthermia and one case of post-anesthetic hepatic necrosis were reported in the clinical trials. These are consistent with the extensive sevoflurane experience in Japan and not unlike other halogenated inhalational anesthetics.

Extensive pre- and postanesthetic laboratory testing of hepatorenal function was performed in the studies submitted to the NDA. While there were occasional episodes of transient hepatic dysfunction (see Dr. Spyker's safety review), there was no evidence of sevoflurane's being more toxic than isoflurane or enflurane except in the case of elderly patients, where there was a statistically higher incidence (4% vs 2%) of transient elevation of liver function tests following sevoflurane. Based on these experiences, the individual clinical reviewers all concluded that sevoflurane was both safe and effective.

**Anesthesia and Life Support Drug Advisory Committee proceedings:**

During the public comment portion of the meeting, Drs. Edmund Eger and Jackie Martin, both consultants for a competing sponsor, presented results of their unpublished research suggesting that the toxic threshold for renal injury in humans from Compound A might occur at a much lower level than previously thought (see Appendix). Furthermore, they questioned the validity of the standard postanesthetic renal function testing which, they felt, was insensitive to the type of proximal tubular damage induced by Compound A in rats.

The committee's deliberations were clearly influenced by these individuals' presentations, even as it discussed the extensive preclinical and clinical safety studies. Ultimately, the committee voted 10-1 to approve the drug with a warning that the Compound A issue is unresolved and that a fresh gas flow rate of 2 l/min should be maintained during clinical anesthesia. This flow rate was shown to result in Compound A levels between 10 and 15 ppm.

**Phase 4 Commitments:**

ALSAC recommended that the Compound A issue be resolved before the 2l/min fresh gas flow rate warning could be removed from the label.

1) It was requested that a primate study be performed utilizing prolonged, progressively increasing exposure to Compound A during sevoflurane anesthesia, with detailed post-anesthetic testing of renal tubular function to include urinary concentrating ability and protein/creatinine ratios.

2) The sponsor committed to completing a clinical study of low-flow general anesthesia with sevoflurane in renally impaired patients, with detailed followup of post-anesthetic renal function, as above.

3) The sponsor committed to developing a safety database for low-flow anesthesia in a large number of patients using standard postoperative renal function tests.

Orig NDA # 20-478  
HFD-007/Div File  
HFD-007/RBedford  
HFD-007/LVaccari  
HFD-502  
HFD-340  
F/T by

RF Bedford 3/22/95  
Robert F. Bedford, MD

Barbara Palomares 3/22/95  
Peer Reviewer

# CLINICAL REVIEW SUMMARY

NDA 20-478      Ultane (sevoflurane)  
Liquid anesthetic for general anesthesia

SPONSOR:          Abbott Laboratories

NDA submitted: July 8, 1994  
NDA received: July 11, 1994

The Clinical Section of this NDA was reviewed by members of the Anesthetic and Life Support Drugs Advisory Committee (ALSAC) and Consults, as well as Robert Bedford, M.D., HFD-007 and Dan Spyker, M.D., HFD-007. The attached document consists of their reviews of the assigned clinical studies by each reviewer..

1.    Renee K. Landesman, M.D., ALSAC  
      Review of seven clinical trials categorized as Metabolism/Safety Studies.
2.    C. Philip Larson, Jr., M.D., ALSAC  
      Review of twelve clinical trials categorized as Adult Inpatient and Outpatient Use of Sevoflurane.
3.    Robert G. Merin, M.D., ALSAC  
      Review of four clinical trials categorized as Cardiac Studies.
4.    Margaret Wood, M.D., ALSAC  
      Review of six clinical trials categorized as Pediatric Studies.
5.    Marie L. Young, M.D., ALSAC  
      Review of six clinical trials categorized as Special Population Studies in Renal and Hepatic Impaired and and the Elderly.
6.    James C. Eisenach, M.D., ALSAC  
      Review of two clinical trials, one for use in Cesarean Section, and a second for effects of sevoflurane on muscle relaxants.
7.    Robert F. Bedford, M.D., Acting Director HFD-007  
      Review of three clinical trials categorized as Neurosurgical Studies. Review of one clinical trial for the use of sevoflurane in adult surgical patients.
8.    Dan Spyker, M.D., Medical Officer HFD-007  
      Clinical Safety Review

The combination of these individual reviews provides the conclusion that the safety and efficacy of sevoflurane has been established.

*Robert F Bedford*

Robert F. Bedford, M.D.  
Acting Director, HFD-007

3/22/95

**MEDICAL OFFICER REVIEW**

NDA # 20,478  
Sevoflurane  
Abbott Hospital Products  
NDA submitted: July 11, 1994  
Reviewer: Renee K. Landesman, M.D.  
September, 1994

**Study # 3**

**Purpose:** Identify the role of cytochrome P450 2E1 in sevoflurane defluorination.

**Investigator:** Evan Karasch, University of Washington

**Study Design:** Open-label, randomized study comparing the production of inorganic fluoride and hexafluoroisopropanol (HFIP) during sevoflurane anesthesia in patients pre-treated with disulfiram to a control group.

Blood concentrations of sevoflurane, and serum and urinary concentrations of inorganic fluoride and hexafluoroisopropanol (HFIP) were determined during and after exposure to the anesthetic.

All treated patients were included in safety and efficacy analyses.

**Results:**

Twenty-two ASA Class I and II patients were exposed to 3.0-4.2 MAC-Hours of sevoflurane anesthesia while undergoing elective surgery. The average MAC exposure was 1.3, with a range of 1.2-1.4. Twelve patients had received a single (500 mg) dose of disulfiram the evening before to surgery; ten patients made up the control group. Duration of surgery was between 136-184 minutes.

The peak serum fluoride concentration in the control group was 59.5  $\mu\text{M}$  3 hours after anesthesia, with a mean peak of 32.3  $\mu\text{M}$ . Seven of the 10 subjects sustained serum fluoride levels of 20  $\mu\text{M}$  or over for 10 to 26 hours.

There was a 3-4 fold reduction in the measured amounts of inorganic fluoride and HFIP excreted in the group pre-treated with disulfiram. Mean renal clearance of total HFIP was not statistically different in the two groups.

Cytochrome P450 2E1 appears to be the predominant isoform responsible for metabolism of sevoflurane in humans.

Based on the HFIP data, the metabolism of sevoflurane is 4.9%.

**Safety:** No clinically significant adverse effects attributable to the anesthetic technique were identified. Vital signs monitoring, hematology, blood chemistry, urinalysis, and physical assessments were evaluated throughout the study and up to 96 hours post-operatively where feasible.

**Study # 4:**

**Purpose:**

Evaluate the production of Compound A in a rebreathing circuit with soda lime using sevoflurane for induction and maintenance of anesthesia in pediatric patients.

**Investigator:** Edward J. Frink, M.D., The University of Arizona

**Study design:** Open-label. Pilot study of three patients using a non-rebreathing circuit at a flow rate of approximately 250 ml/kg/min. Nineteen patients in group 2 received sevoflurane using a 2L/min. rebreathing circuit containing soda lime (Sodasorb).

No patients were excluded from analysis.

**Results:**

Patients in the soda lime group ranged in age from 0.2-7.5 years, and in weight from 4.1 to 27.6 kg. Surgery lasted from 52-521 minutes, with an anesthetic exposure from 1-14 MAC-Hours. The average MAC was 1.09, with a range of 0.7-1.4.

Maximum concentration of Compound A in the inspiratory gases ranged up to 14 ppm.

**Safety:** Physical examination, vital sign monitoring, and laboratory data showed no clinically significant abnormality attributable to the anesthetic technique.

**Study # 5:**

**Purpose:**

Evaluate the effect of phenobarbital pre-treatment on defluorination of sevoflurane.

**Investigator:** Jeffrey Apfelbaum, M.D., Pritzker School of Medicine.

**Study Design:** Open-label, randomized (1:1). Pre-treatment (phenobarbital, approximately 2 mg/kg, taken orally at bedtime)

for a minimum of 14 days.

Results:

Sixteen healthy males, ages 23-34 years completed the study. Anesthesia exposure 3 MAC-Hours at an average of 1 MAC. Two patients were discontinued prior to anesthetic exposure - one for non-compliance, and one for an allergic reaction (rash) to the phenobarbital.

Antipyrine elimination rate constant and clearance were significantly higher in the phenobarbital group than the placebo group.

Maximum serum fluoride concentration measured was  $47.6\mu\text{M/L}$ ; mean inorganic fluoride  $\text{C}_{\text{max}}$  was 23% higher ( $p=.047$ ) in the phenobarbital + sevoflurane group compared to the placebo + sevoflurane group. Elimination rate constant, area under the curve, cumulative amount excreted, and renal clearance were not significantly different between the two groups.

Safety: No safety issues attributable to the anesthetic exposure were identified.

Study # 6:

Purpose: Evaluate the metabolism and degradation products of sevoflurane in adult patients when administered via a low flow circle absorption system.

Investigator: Edward J. Frink, M.D., University of Arizona

Study Design: Open-label, uncontrolled. Low flow (<1 L/min) circle absorption using soda lime ( $N=12$ ) or baralyne ( $N=8$ ). Surgeries anticipated to be from 3-8 hours duration.

Results:

All twenty patients completed the study and were included in the safety and efficacy analyses.

Degradation products were not obtained for the first four patients due to problems developing the assay method.

Duration of surgery ranged from 84 minutes to 450 minutes, with a mean of 210 minutes. The anesthetic exposure ranged from 0.8-5.4 MAC Hours, with a the MAC ranging from 0.2-0.8. The mean MAC for the soda lime group was 0.4; for the baralyne group 0.5.

The only degradation product detected in the circuit was Compound A. The highest level of Compound A in the inspired limb was 60.8ppm (mean 17.15) in the Baralyne group, compared to 15.2ppm (mean 6.95) in the Soda Lime group. This was not statistically

significant however.

Plasma fluoride concentrations peaked within two hours post anesthesia in all except one patient, whose level peaked at four hours. Mean C<sub>max</sub> was 41.28, with a range between 20.8-101.2. The fluoride half-life by log-linear regression of the normalized concentration was 11.0 hr. Ten patients maintained fluoride concentrations over 20 $\mu$ M for over ten hours. An unusually high baseline level of fluoride (8.13-16.74 $\mu$ M) was noted in five of the 20 patients.

Safety: Physical observation, laboratory data, and vital sign monitoring did not identify any unusual safety concerns attributed to the anesthetic technique.

Implications for Labeling:  
Under CLINICAL PHARMACOLOGY:

The paragraph concerning the concentrations of Compound A should include the statement "The maximum level of Compound A measured in the anesthesia circuit was 60.8 ppm."

Study # 7:

Purpose: Determine the concentration of Compound A in adults using sevoflurane in a low flow rebreathing circuit.

Investigator: R. Jones, M.D., St. Mary's Hospital, London

Study Design: Open-label, uncontrolled, randomized. After twenty minutes of sevoflurane administered at a fresh gas flow rate of 4L/min, 16 patients continued at 0.5L/min, and 15 patients continued the anesthetic at a fresh gas flow rate of 2 L/min for the remainder of the procedure.

Results:

All thirty-one patients were included in the safety and efficacy analyses.

The mean MAC-Hours of anesthesia was 1.73 vs 1.65 for the two groups, with a range of 0.6-3.9. The average MAC exposure ranged from 0.5-1.2, with a mean of 0.81 and 0.88.

The maximum concentration of Compound A in the inspiratory limb of the circuit ranged from 10-32 ppm, with no significant difference between the two groups.

Safety:

No clinically significant adverse effects attributed to the

anesthetic technique were seen.

Study 8:

Purpose:

Evaluate the effects of repeat exposures to sevoflurane on safety, fluoride concentrations and hepatic response.

Investigators:

Multicenter - 4 sites.

George B. Bikhazi, M.D., Jackson Memorial Hospital, Miami, FL  
1 patient, 3 exposures

Robert F. Finnegan, M.D., University of Texas Health Science Center, Houston, TX

15 patients, 13 second and 4 third exposures

Charles B. Hantler, M.D., University of Texas Health Science Center, San Antonio, TX

7 patients, 4 second and one third exposure

Roger I. Kaiser, Jr., M.D., Erie County Medical Center, Buffalo, NY

2 patients, one second exposure, no third exposures.

Study Design:

Multicenter, open-label. Patients undergoing 2-3 surgical operations of at least 1 hour duration, within a 2 week period.

Results:

For the twenty-five patients in the first exposure group, a mean dose of 0.85 MAC-Hr was administered over a mean duration of 1.67 hours. The mean fluoride C<sub>max</sub> was 29.2  $\mu\text{M}$  with a maximum value of 80.9  $\mu\text{M}$ .

The nineteen patients with a second exposure received a mean dose of 2.17 MAC-Hr over a mean duration of 3.67 hours. Mean fluoride C<sub>max</sub> was 42.5  $\mu\text{M}$  with a maximum level of 111  $\mu\text{M}$ .

Six patients were exposed a third time to a mean dose of 1.25 MAC-Hr over a mean duration of 2.72 hours. Mean fluoride C<sub>max</sub> was 49.9  $\mu\text{M}$  with a maximum of 99.5  $\mu\text{M}$ .

The fluoride C<sub>max</sub> after the second and third exposure were significantly different from the first exposure. Anesthetic exposure was 2.17 MAC-Hr and 2.72 MAC-Hr for the second and third exposures compared to 0.85 MAC-Hr for the first exposure. The higher levels thus are at least partly due to the longer exposure.

Patient # 61, a 36 yo M, reached a C<sub>max</sub> of 80.9  $\mu\text{M}$  after the first exposure, 87.1  $\mu\text{M}$  after the second exposure, and 99.5  $\mu\text{M}$  after the third exposure. His serum fluoride was still at 34.1  $\mu\text{M}$

67 hours after the initial procedure (244 minutes and 1.8 MAC-Hr).

Patient # 5, a 56 yo M, had Cmax levels of 47.9, 111, and 65.8  $\mu\text{M}$  after his respective exposures. His serum levels were still at 34.1  $\mu\text{M}$  39 hours following his second exposure (769 minutes, 9.67 MAC-Hr), and 29.5  $\mu\text{M}$  92 hours following the third exposure (0.71 MAC-Hr).

Both patient # 5 and # 61 were electrical burn patients, and they were the only two burn patients in the series.

Safety:

No clinically significant adverse effects other than fluorosis were attributed to the anesthetic. No unexpected changes in renal function were observed.

Implications for Labeling:

Under CLINICAL PHARMACOLOGY:

The sentence concerning the inorganic fluoride concentrations should end as follows ".....and return to baseline concentrations within 48 hours post anesthesia in the majority of cases".

Under RENAL OR HEPATIC FUNCTION:

The second paragraph should read:

"Based of the incidence and magnitude of changes in serum creatinine, no evidence for increased risk of developing renal dysfunction was found with sevoflurane.

Serum fluoride levels increased with duration and concentration of exposure to sevoflurane. Peak serum fluoride levels up to 111  $\mu\text{M}$  were seen, and a level of 29.5  $\mu\text{M}$  was seen as late as 92 hours post exposure.

A 25% reduction in maximum urine-concentrating ability has been seen following enflurane anesthesia where the kidneys were exposed to a mean peak serum inorganic fluoride of 33.6  $\mu\text{M}$ , with values above 20  $\mu\text{M}$  for 18 hours. The clinical implications of this are not clear.

Study # 9

Purpose:

Evaluate the effects of repeated exposure to sevoflurane in pediatrics.

Investigators:

Multicenter (4 investigators, 6 sites)

Study Design:

Open-label study in pediatric patients having two anesthetic procedures within 28 days, each at least one hour.

Results:

Thirteen patients entered the study. Ten patients had a second exposure. The second exposure was refused by the parents for the first three patients.

The mean MAC-Hrs for the first exposure was 3.1 at an average 0.8 MAC; the second exposure was a mean 2.6 MAC-Hrs at 0.8 MAC.

There was no statistical difference in the Cmax fluoride between the two exposures.

Safety:

No safety concerns associated with the anesthetic technique were identified by routine laboratory and physical assessments throughout the study.

**MEDICAL REVIEW**

**NDA 20-478**

**NDA submitted: July 11, 1994**

1

**NAME:** Sevorane (Sevoflurane)  
**REVIEWER:** C. Philip Larson Jr., M.D.   
**REVIEW DATE:** September 1994  
**RESUME:** MAC of Sevoflurane in Elderly and Young Adult Patients  
**STUDY NUMBER:** 2 (Pivotal study)  
**PROTOCOL NUMB:** SEVO 92-034

**BACKGROUND:**

The minimum alveolar concentration (MAC) for sevoflurane has been determined by two groups of investigators, and the values published. The first study was performed in Japanese patients ranging in age from 30 to 59 years, and the MAC value was reported as 1.7% (Anesthesiology, 1987; 66:301-303). The second study was performed in Americans ranging in age from 30 to 48 years, and the MAC value was reported as 2.05% (Can J Anaesth, 1988; 35:153). The sponsor also states that it has been demonstrated that the MAC for sevoflurane is greater in children than adults, but the data documenting this claim have not been published in peer reviewed journals. Study 2 (Sevo 92-034) was designed to determine whether sevoflurane, like halothane and isoflurane has an age-related decrease in MAC as age increases; and the magnitude of the decrease in MAC in young adults and elderly when nitrous oxide 60% was added to the inspired gas mixture.

**METHODS:**

A total of 56 surgical patients was studied, half of whom ranged from 18-35 years and the other half from 70-87 years. They were randomly assigned to receive either sevoflurane in air or nitrous oxide (60%). The patients did not receive any premedication; and anesthesia was induced with the patients breathing sevoflurane 2% and nitrous oxide 60%. Once endotracheal intubation had been completed using succinylcholine or vecuronium, and the end-tidal sevoflurane concentration was stable for 15 min (Datex gas analyzer), a skin incision was made and purposeful movement noted. Grimacing or straining were not considered purposeful movements. Depending upon the patient response, the sevoflurane alveolar concentration was either increased or decreased 0.25% in the next patient to be studied. All data were recorded by a trained, unblinded, independent observer. Three patients in the sevoflurane/air group were excluded from the MAC study because two received other medication (morphine, N<sub>2</sub>O), and in one the vaporizer malfunctioned. Safety was determined by standard monitoring during anesthesia, by laboratory analysis (hematology, blood chemistry, and urinalysis) postoperatively, and by 24 hr followup questionnaire. Appropriate statistical analyses were performed using logistic regression and one and two way ANOVA.

**RESULTS:**

MAC showed a progressive decrease with age, being 2.9% at 18 years, 2.2% at 35 years, 1.5% at 70 years and 1.3% at 87 years. By extrapolation, the MAC at 42 years was 2.05%. The MAC values were decreased by 40-50% by the addition of nitrous oxide 60% (1.6-1.2% in young adults, and 0.8-0.6% in elderly).

**EFFICACY ASSESSMENT:**

Anesthesia was easily and smoothly induced using sevoflurane/nitrous oxide by inhalation, and sevoflurane either alone or with nitrous oxide provided complete amnesia and analgesia. The MAC values were similar to those reported in the prior studies cited above.

**SAFETY ASSESSMENT:**

Sevoflurane proved to be safe in this study. The inhalation induction and recovery were uneventful, and generally devoid of respiratory or circulatory complications. One 79 y.o. patient developed a myocardial infarction two days postoperatively, one 26 y.o. patient developed ST depression late in the anesthetic procedure, and one 62 y.o. patient developed protracted nausea postoperatively. While changes in clinical chemistries occurred, none were of sufficient magnitude to be clinically meaningful.

**CONCLUSIONS FROM STUDY:**

The MAC for sevoflurane is 2.9% at age 18 and decreases progressively to 2.05% at age 42 and 1.3% at age 87. The values are decreased by 40-50% by the addition of nitrous oxide 60%. The drug is an effective anesthetic, and proved to be safe in this patient population.

**RECOMMENDATION REGARDING LABELING:**

The MAC value listed on page 9 for a 40 year old adult should be . The table on page 28 should read:

age	sevoflurane % in O <sub>2</sub>	sevoflurane% in N <sub>2</sub> O 60%
-----	---------------------------------	--------------------------------------

**NAME:** Sevoflurane (Sevoflurane)  
**REVIEWER:** C. Philip Larson Jr., M.D.  
**REVIEW DATE:** September 1994  
**RESUME:** Maintenance of Anesthesia: Sevoflurane vs Isoflurane in Inpatients  
**STUDY NUMBER:** 10 (Pivotal study)  
**PROTOCOL NUMB:** SEVO 92-003

#### **BACKGROUND:**

This study was designed to compare the maintenance of anesthesia, the rapidity and ease of emergence and recovery, the drug metabolism, and the safety in surgical patients administered either sevoflurane or isoflurane as the primary anesthetic.

#### **METHODS:**

A total of 555 adult surgical patients undergoing operations of at least one hour duration were studied in one of 12 institutions, seven of which were in the US and the remainder in Europe. The patients ranged in age from 18-92 years and were assigned ASA Class I-III. They were randomly assigned to receive either sevoflurane (272 pts) or isoflurane (283 pts) with nitrous oxide (60-70%). The patients received standard premedicant drugs and induction agents. Endotracheal intubation was facilitated using succinylcholine or vecuronium, and in some patients fentanyl by bolus or infusion was administered during maintenance anesthesia. The inspired sevoflurane concentration was less than 3%, and the inspired isoflurane concentration averaged 1.8%. End-tidal gas concentrations were monitored continuously using a Datex gas analyzer. The mean MAC hours of anesthesia were shorter in the sevoflurane group (1.3) as compared to the isoflurane group (1.6). Standard patient monitoring included EKG, BP, PS, pulse oximeter, temp, capnography, and n-m blockade. A trained, unblinded observer recorded all of the data.

Efficacy of sevoflurane compared to isoflurane was determined by its ability to maintain surgical anesthesia, the rapidity and ease of patient emergence and recovery, need for postoperative analgesics, and rate of recovery of normal psychomotor performance. Comparative safety was determined by standard monitoring during anesthesia, by postoperative evaluation of all adverse experiences, by laboratory analysis (hematology, blood chemistry, and urinalysis) postoperatively, and by 24 hr followup questionnaire. Appropriate statistical analyses were performed.

#### **EFFICACY ASSESSMENT:**

Anesthesia was as easily and readily maintained with sevoflurane/nitrous oxide as with isoflurane/nitrous oxide as evidenced by similar low (<5%) incidences of cardiovascular changes, and no evidence of recall on postoperative evaluation. Postoperatively, time to emergence (open eyes on command), time to response to commands (squeeze hand), time to orientation to name, birthdate and age, and time to need for postoperative analgesics were 5-10 min shorter for sevoflurane than for isoflurane. These differences, which were significant, may be due in part to the fact that the average MAC hours value was significantly shorter for sevoflurane than for isoflurane. It is of interest that the time from termination of the

anesthetic to extubation of the trachea, and total time until eligible for discharge from the recovery room were not different between the two drugs. Finally, the degradation in psychomotor function was less for sevoflurane than isoflurane in the first 15-90 min postoperative.

#### SAFETY ASSESSMENT:

The overall incidence of adverse experiences was the same for patients given sevoflurane (95%) as for those given isoflurane (92%). The most common adverse experiences were somnolence (33%) and nausea (50%) in both groups. Postoperative fever and tachycardia were significantly more frequent following isoflurane (21 and 4%) than following sevoflurane (14 and <1%). While some significant changes in blood chemistries were observed, none were clinically important. Three patients administered sevoflurane developed peak serum inorganic fluoride concentrations greater than 50 uM (52, 53, and 63 uM), but the increases were transient and did not affect renal function.

Five patients in the sevoflurane group had serious adverse experiences, four of which (postoperative burning in legs-1, pulmonary embolism-2, gall bladder leakage-1) seemed unrelated to the anesthetic. One patient undergoing an orthopedic procedure developed a sudden increase in end tidal carbon dioxide. A diagnosis of malignant hyperthermia was made, the anesthetic was discontinued, and the patient was treated with dantrolene. Postoperatively the CPK increased to 9941 IU/l, and a muscle biopsy was interpreted as MH susceptible. Six patients in the isoflurane group developed operative or postoperative surgical complications that were unrelated to the anesthetic.

#### CONCLUSIONS FROM STUDY:

Sevoflurane is as efficacious and safe as isoflurane when administered under conditions similar to this study.

#### RECOMMENDATION REGARDING LABELING:

While recovery of some variables (emergence, ability to follow commands, and orientation) was more rapid from sevoflurane than isoflurane anesthesia, the differences were not clinically important. Furthermore, the most important variables, time to extubation and time to discharge from the recovery room were not significantly different between the two groups. Finally, the differences that were significant may be due in part to the fact that the mean MAC hours value was less for sevoflurane than isoflurane.

Page 23, paragraph 3: Since one patient in this study developed MH, I believe that the first sentence of this paragraph should read "In susceptible individuals, potent inhalation anesthetic agents, including sevoflurane may trigger...etc"

IND #  
 NAME: Sevorane (Sevoflurane)  
 REVIEWER: C. Philip Larson Jr., M.D.  
 REVIEW DATE: October 1994  
 RESUME: USE OF SEVOFLURANE IN PATIENTS

**BACKGROUND:**

The following studies, 11 through 14 evaluate the use of sevoflurane in a variety of patients and anesthesia and surgical conditions.

**Study 11: COMPARISON WITH PROPOFOL**

This study was designed to compare the induction and maintenance of anesthesia with sevoflurane vs. propofol in healthy (ASA 1 & 2) patients who were undergoing surgical procedures of 1-3 hrs in length. A total of 186 patients in four institutions (3 US, 1 Canada) were randomly assigned to receive either an inhalation induction and maintenance with sevoflurane, or induction and maintenance with propofol. Both groups received N<sub>2</sub>O 60-70%, and fentanyl 2 ug/kg prior to induction. The sevoflurane concentration varied from 0.25 to 2.7% (average 1.4%), and the propofol dose ranged from 20 to 4300 mg with an average infusion rate of 7 mg/kg/hr. The patients underwent a wide variety of surgical procedures, but the most common operations were back or GI surgery or hysterectomy.

**Efficacy Assessment:**

Times for induction and intubation of the trachea were significantly longer (1 and 2 min) for sevoflurane, but times for emergence, extubation, response to commands, orientation and first p/o analgesia were significantly shorter (4, 4, 3, 5 and 11 min) for sevoflurane than propofol. While these times are clinically significant, they are not clinically important. Furthermore, it is impossible to know if the two anesthetics were compared at equipotent doses, since there were no measurements of anesthetic depth. Also, most of the patients received nondepolarizing neuromuscular blocking drugs which would lessen ability to detect need for analgesic drugs.

**Safety Assessment:**

Nausea and vomiting were the most common p/o complications with the incidence being about 40% for both groups of patients. Hypotension occurred with less frequency with sevoflurane than with propofol, but bradycardia occurred with greater frequency (10 vs. 2%). Four serious adverse experiences were reported with sevoflurane, and all were rated as being unrelated to the drug. However, from my reading of the case reports, I believe that two events may have been related to the drug. One case, Patient 22 developed bradycardia to the low 50's while undergoing a cystocele/rectocele repair. Atropine 0.4 mg was administered, and shortly thereafter the patient went into 5 sec of asystole. Sevoflurane was discontinued and isoflurane started. No further episodes of bradycardia occurred. Since sevoflurane is associated with bradycardia in about 10% of patients, it is possible that it contributed to the adverse event. Furthermore, those administering the anesthetic must have thought so or they would not have

switched agents. Another patient, no 1001 developed anuria postop following a total splenectomy for multiple myeloma and hereditary spherocytosis. While the creatinine was elevated preop (151 uM/l), the permanent need for dialysis postop may have been due in part to the use of sevoflurane. I do not see how the drug can be exonerated in this patient.

## STUDY 12: COMPARISON WITH ISOFLURANE IN OUTPATIENTS

This study compared the anesthetic and recovery effects of equianalgesic doses of sevoflurane and isoflurane in 500 ASA 1 and 2 patients undergoing surgical procedures as outpatients in 11 institutions, 6 in the US and 5 in Europe. The patients ranged in age from 18 to 84 (av 36) years, and about 66% were women. The most common operations were diagnostic laparoscopy, knee arthroscopy, and laparoscopic sterilization. About 50% of patients received midazolam and 36% fentanyl for premedication. Anesthesia was induced with either propofol or thiopental, and nitrous oxide 50-70% was used in virtually all patients. About 70% of patients received a nondepolarizing neuromuscular blocking drug, usually vecuronium. While the MAC concentrations of sevoflurane and isoflurane varied considerably during the anesthetic, the mean MAC concentration for sevoflurane was significantly lower (0.61 v. 0.70 MAC, MAC assumed to be 2.05% for sevoflurane and 1.15% for isoflurane), but the duration of exposure was longer so the MAC-hours were similar for the two drugs (0.64 v. 0.66).

### Efficacy Assessment:

While the times to emergence, response to commands and orientation were significantly shorter for sevoflurane, they were not clinically important differences (1, 1, and 2 min). While not statistically significant, the times to extubation of the trachea and ability to walk without dizziness were shorter for isoflurane (3 and 40 min), even though the MAC values for isoflurane were greater. The average times for discharge from hospital were not significantly different for the two drugs. Postoperatively, subjective feelings, psychomotor performance, analgesic requirements, and modified Aldrete scores were not different between the two drugs.

### Safety Assessment:

The most often observed postoperative complications were cough, (47%), nausea (45%), and vomiting (23%) with no significant differences between the two drugs. Bradycardia (not defined) was four times more common (12 pts) with sevoflurane than isoflurane (3 pts). The incidence of drug-related adverse experiences was the same for the two drugs (22%). Fourteen patients given sevoflurane exhibited severe postoperative complications (pain, vomiting, syncope) all of which did not seem to be related directly to the administration of this drug. An equal number of patients given isoflurane exhibited the same complications postoperatively. A significantly higher percentage of patients given sevoflurane (28% v. 19%) demonstrated a decrease in hemoglobin concentration postoperatively, and one patient had a decrease in platelet count from 163 to 65 p/o. It is not possible to determine whether these changes were due to the drug or other events that transpired during or early after surgery.

**STUDY 13: COMPARISON OF RECOVERY WITH ISOFLURANE**

This study was designed to compare the recovery and safety of sevoflurane with isoflurane in 75 ASA 1 & 2 patients undergoing routine surgical procedures, the most common being hysterectomy. Fifty of the patients received sevoflurane, and 25 isoflurane. The average sevo concentration was 2.6 or 21% above MAC, while the average isoflurane concentration was 1.67% or 41% above MAC. While the MAC-hours were not different, the average MAC exposure was (sevo 1.27 v. isoflurane 1.46. Both drugs were administered with oxygen; no nitrous oxide was used. Most of the patients received midazolam premedication, about half received fentanyl, and virtually all patients received thiopental for induction of anesthesia and vecuronium for muscle relaxation.

**Efficacy Assessment:**

The times to extubation, emergence, and first requirement for analgesia were significantly shorter for sevo (8, 8 and 13 min) than for isoflurane (19, 20, and 27 min). The sevo patients were more awake, alert and oriented at emergence than the isoflurane patients. A blood sevo pharmacokinetic analysis showed a typical value for t 1/2 a of about 1 hr and a Cmax of 511 uM. The typical fluoride values were t 1/2 of 10.4 hrs and C max of 31 uM.

**Safety Assessment:**

About 33% of the patients in both treatment groups developed nausea which was not serious. One patient in the sevo group emerged from anesthesia with bradycardia that progressed to asystole which returned to sinus rhythm after several chest compressions. The investigator assigned the cause to the administration of neostigmine, but because there is accumulating evidence that sevo is associated with bradycardia in some patients, it may have contributed to the asystole. Seven sevo patients had peak inorganic fluoride concentrations greater than 50 uM (50 to 75 uM) all on the day of surgery while none of the isoflurane patients reached these values. None of these patients evidenced any abnormalities in BUN or creatinine postoperatively.

**Conclusion:**

While the investigators concluded that sevo has a faster recovery, the differences in dose may explain in part or entirely why the sevo patients emerged from anesthesia more rapidly. I was not able to confirm that there were fewer adverse respiratory effects with sevo than isoflurane. No serious injury was observed despite the level of inorganic fluorine in 7 patients. Clearly inorganic fluoride levels are higher in sevo patients, but renal impairment does not seem to result from this.

**STUDY 14: COMPARISON OF RECOVERY WITH ISOFLURANE WITH AND WITHOUT PROPOFOL**

This study performed at one institution was designed to evaluate the recovery phase of sevo with isoflurane in patients when intravenous induction agents are or are not used. All patients were women ASA 1 or 2, most of whom were undergoing a hysterectomy. They all received fentanyl prior to induction of anesthesia. Patients were divided into three groups of 25 each: Gp

A received sevo by mask induction; B received propofol induction and sevo anesthesia; and C received propofol induction and isoflurane anesthesia. All received 60-70% nitrous oxide. The MAC concentration was significantly greater for the isoflurane patients (0.6 MAC) than for the other groups (0.4 MAC); and the MAC-hours were greater for the isoflurane group (1.6 v. 1.1 and 1.0). All of the patients received succinylcholine, vecuronium and most received morphine during surgery. I was not able to determine the mean dose or range of propofol used for induction.

#### Efficacy Assessment:

Induction time was shorter with propofol/sevo than propofol/iso or sevo alone. Whether this was due to the difference in uptake of the two volatile agents, or to a difference in dose of propofol could not be determined from the data. Times to extubation and emergence were significantly shorter (5-7 min) with sevo than with iso (9-11 min). Induction and emergence were smooth and uneventful with all three techniques.

#### Safety Assessment:

The maximum concentration of inorganic fluoride occurred about 2 hrs after conclusion of anesthesia and were 47 and 42  $\mu\text{M}$  in the sevo groups and 16  $\mu\text{M}$  in the iso group. The mean concentrations were 25, 19 and 2  $\mu\text{M}$ . There were no significant differences among the groups in values of BUN or creatinine postop. The most common postop complication was nausea which occurred in about 50% of all patients. No other serious adverse experiences occurred in any of the groups.

#### Conclusion:

This study demonstrates that sevo can be used safely and effectively for mask induction in adults. The finding of a more rapid emergence and extubation with sevo, while statistically significant is not clinically significant, and may have been due in part or wholly to the difference in dosage of the sevo v. iso groups.

#### SUMMARY OF FOUR STUDIES:

From these four studies we can conclude:

1. Sevo can be used effectively and safely for mask induction anesthesia.
2. Recovery from sevo is more rapid than with isoflurane, but the differences are not clinically important.
3. It isn't clear from these studies whether recovery from sevo is more rapid because of its lower solubility or because it was used in lower doses.
4. Sevo causes bradycardia in some patients, which may be serious.
5. Sevo increases levels of inorganic fluoride above those observed with isoflurane, but no patients exhibited renal insufficiency as evidenced by abnormal values of BUN or creatinine.

IND #  
 NAME: Sevorane (Sevoflurane)  
 REVIEWER: C. Philip Larson Jr., M.D.  
 REVIEW DATE: November 1994  
 RESUME: USE OF SEVOFLURANE IN PATIENTS

**BACKGROUND:**

The following studies, 15 through 20 evaluate the use of sevoflurane in a variety of patients and anesthesia and surgical conditions.

**Study 15: COMPARISON WITH ISOFLURANE IN NORMAL, ELDERLY AND OBESE PATIENTS UNDERGOING NON-CARDIAC SURGERY AND PATIENTS UNDERGOING CARDIAC SURGERY**

This study was designed to compare sevoflurane vs. isoflurane anesthesia in ASA 1-3 patients who were undergoing surgical procedures of 1-6 hrs in length. A total of 450 patients in 10 US institutions were randomly assigned in a ratio of 4:1 to receive either sevo or isoflurane. Of this group, 25 underwent cardiac surgery, and 425 non-cardiac surgery, with two subpopulations of patients, one being elderly (>65 yrs) 53 pts, and the other being obese (>100 kg) 63 pts. Of the 450 pts, 359 received sevo (80%) and 91 (20%) received isoflurane.

The cardiac patients all had good left ventricular function. In this group anesthesia was induced with fentanyl and etomidate, and maintained with either sevo 3% (20 pts) or isoflurane 1.8% (5 pts) with nitrous oxide until bypass. Wash-in and wash-out studies of each drug over 30 min were performed during bypass.

**Efficacy Assessment:**

Times to extubation, emergence and first analgesia were significantly shorter for sevoflurane (9, 8, and 38 min), than isoflurane (14, 12, and 45 min), but the time for eligible discharge from the recovery room was not different. The cumulative Aldrete score for respiration and consciousness was higher for the sevo than for the iso patients, but were equal at the time of discharge. The elderly and obese pts did not have significantly different times than the other pts. The wash-in and wash-out curves in cardiac patients were more rapid for sevo than iso, but the differences were not statistically significant.

**Safety Assessment:**

Emergence complications were trivial in both groups. A significantly higher percentage of patients given sevo (42-45%) had postop nausea compared to iso (29%). In the 139 patients in whom inorganic fluoride was measured, mean Cmax was 31 uM, Tmax was 122 min, and t1/2 was 9 hrs. The values were not significantly higher in the obese or elderly. Ten patients in the sevo group had inorganic fluoride concentrations >50 uM; none showed any evidence of renal insufficiency postop. The incidence of bradycardia was not greater in the sevo group. One cardiac patient given sevo died on p/o day 1, probably unrelated to sevo.

**Conclusion:**

1. While the recovery from sevo was faster, the differences from iso were not clinically important. Furthermore, most or all of the faster recovery from sevo may have been due to the fact that the dose of iso was greater (MAC-hours 33% > and average MAC exposure 20% >). Because of the higher sevo dose, the sponsor cannot conclude from this study that sevo has better recovery characteristics than iso.

2. None of the sevo patients developed clinical renal insufficiency despite the higher levels of inorganic fluoride compared to the iso group.

**STUDY 16: COMPARISON WITH ENFLURANE**

This study compared the anesthetic and recovery effects of equianalgesic doses of sevoflurane and enflurane in a 2:1 ratio in 277 ASA 1-3 patients undergoing surgical procedures as inpatients in 9 institutions in Europe. The patients ranged in age from 18 to 88 (av 54) years, and were equally divided in gender. The most common operations were bowel resection for cancer and disk surgery. All of the patients received fentanyl 2 ug/kg during induction, and many received a fentanyl infusion during surgery at a rate of 1-3 ug/kg/hr. All patients received vecuronium for relaxation, and nitrous oxide 60%. The unique feature of this study was the fact that 25% of the patients were administered sevo or enflurane via a nonbreathing system. In the remainder, a conventional circle system was used. The mean MAC concentration (0.47 v 0.44) and MAC-hours (1.9 v 1.8) were not significantly different in the two groups.

**Efficacy Assessment:**

While the times to emergence, response to commands and orientation were shorter for sevoflurane, the differences were not statistically significant. The average times for discharge from hospital were not significantly different for the two drugs. The fact that the differences were not statistically significant may be due in part to the use of fentanyl infusions in many of the patients.

**Safety Assessment:**

The most often observed postoperative complications were cough, (25%), nausea (25%), and bradycardia (16%) with no significant differences between the two drugs. The C<sub>max</sub> for sevo was significantly greater (32, range 7-114 uM) than for enflurane (22, 9-45 uM); and the T<sub>1/2α</sub> was significantly shorter (97 v. 173 min). Ten patients in the sevo group had serum inorganic fluoride concentrations of >50 uM/l, but none evidenced any impairment in renal function. Only 2 of the 10 patients evidenced any increase in BUN or creatinine postop. Five patients evidenced mild to moderate increases in BUN or creatinine following sevo, but none had peak fluoride concentrations above 50 uM. There were no significant changes in mean BUN or creatinine levels in either group. Thirteen patients in the sevo group had mild to moderate increases in SGOT or SGPT postop while only 4 patients in the enflurane group showed similar increases. None of these patients demonstrated any sequelae from these changes.

**Conclusion:**

1. It would be helpful to know from the sponsor whether there were any differences in postop adverse events such as higher inorganic fluoride, BUN, creatinine or SGOT-SGPT levels in patients in whom a conventional circle was used compared to those administered sevo by a nonbreathing system.

**STUDY 17: COMPARISON WITH PROPOFOL**

This study was designed to compare the maintenance, recovery and safety of sevoflurane with propofol in 52 ASA 1 & 2 patients undergoing routine surgical procedures of up to 3 hrs duration in one institution in Austria. All but one of the patients were female, most of whom underwent breast, gallbladder or thyroid surgery. Anesthesia was induced with propofol with both groups, following which half received sevo at an average concentration of 1% (range 0.7-1.3%), and the other half received propofol by continuous infusion at an average rate of 6.5 mg/kg/hr (range 4-9) or a total dose of 521 mg (range 210-908). Both groups received nitrous oxide 60-70%. A nonbreathing system was used in 4 of the sevo and 3 of the propofol patients; a circle system was used in the rest. The mean duration of anesthesia was not significantly different between the two groups (82 v. 74 min).

**Efficacy Assessment:**

The times to emergence and orientation were significantly longer for sevo (9 and 13 min) than for propofol (7 and 9 min), but the differences are not clinically important. No other differences were observed during maintenance or emergence from anesthesia between the two groups. There were no significant differences in subjective feelings (visual analog scale) or digital substitution test scores up to 120 min postop between the two groups.

**Safety Assessment:**

There were no serious complications in either group that could be assigned to the anesthetic drugs used. The incidence of nausea (35%) and bradycardia (23%) following sevo were similar to values reported in other studies. Four patients in each group had increases in SGOT-SGPT, creatinine, and/or BUN values postop which may have been due to the use of the anesthetic drugs; but none of these patients evidenced any adverse sequelae postop. No studies of inorganic fluoride levels were done.

**Conclusion:**

1. The maintenance and recovery from sevoflurane anesthesia was not clinically different from propofol anesthesia in this group of patients.

2. It would be helpful if the sponsor could compare postop laboratory values between those patients who did not rebreath anesthetic and those who did, although the number in the former category is so small that any differences would not be significant.

**SUMMARY OF THREE STUDIES:**

From these three studies we can conclude:

1. Concentrations of inorganic fluoride are higher following sevoflurane than enflurane or propofol, but the levels attained which are occasionally above 50 uM/l do not appear to cause any renal impairment.
2. There was no correlation between those patients who had increases in serum inorganic fluoride levels and those who had postop increases in BUN or creatinine.
3. Some patients who received sevo had increases in SGOT or SGPT or both. The significance of these changes is unclear.
4. In two of the studies, some of the patients were administered sevo via a nonrebreathing circuit. Unfortunately, the sponsor does not distinguish whether use of this anesthetic system affected the results compared to a circle system.

IND #  
 NAME: Sevorane (Sevoflurane)  
 REVIEWER: C. Philip Larson Jr., M.D.  
 REVIEW DATE: November 1994  
 RESUME: USE OF SEVOFLURANE IN PATIENTS

**BACKGROUND:**

The following studies, 19 and 20 evaluate the use of sevoflurane in a variety of patients and anesthesia and surgical conditions.

**Study 19: COMPARISON WITH ISOFLURANE IN PATIENTS UNDERGOING AMBULATORY SURGERY**

This study was designed to compare sevoflurane vs. isoflurane anesthesia in ASA 1- 2 patients who were undergoing ambulatory surgical procedures of less than 1 hr in length. A total of 246 patients in 5 US institutions were randomly assigned in a ratio of 60:40 to receive either sevo or isoflurane. Eighty percent of patients were women; 70% of operations were on the female genital tract. In all patients anesthesia was induced with propofol 2 mg/kg and fentanyl 1 ug/kg, succinylcholine was used for tracheal intubation, and if additional relaxation was needed, vecuronium 0.04 mg/kg was administered. Both groups received nitrous oxide 60%. The duration of operation was significantly shorter for the sevo patients than the isoflurane patients (38 v. 46 min), so the MAC-hours were significantly less for the sevo v. the isoflurane patients (0.57 v 0.76).

**Efficacy Assessment:**

Times to emergence, response to commands, orientation, and ability to sit up without nausea or vomiting were significantly shorter for sevo (7, 7.5, 9 and 51 min), than isoflurane (9, 10, 12 and 62 min), but the times for eligible discharge from hospital were not different. Aldrete scores for activity and consciousness were higher on admission to the PAR for the sevo than for the iso patients, but were equal at the time of discharge. Subjective feelings (visual analog scale) and psychomotor performance (digital symbol substitution test) were similar in the two groups.

**Safety Assessment:**

The most common postop complication was nausea which was significantly less with sevo than isoflurane (36 v 51%), but one patient in the sevo group had protracted nausea (12 hrs) which the investigator thought was probably due to sevo. The incidence of postop somnolence was significantly less with sevo than isoflurane (15 v. 26%). Bradycardia was not more common in the sevo group, but one sevo patient with a history of vagal reactions (?) developed sinus arrest for 20 sec and hypotension for 2 min that required atropine, ephedrine and 8-10 cardiac compressions to resolve. While the investigator did not believe that this event was related to the use of sevo, it is not possible to exclude that this event may have been caused by sevo from the data provided. No important mean changes in laboratory values were observed, including no changes in SGOT-SGPT, BUN or creatinine. Inorganic fluoride values were not measured.

### Conclusion:

1. Sevoflurane provides an anesthetic state and recovery that is similar to that for isoflurane in this outpatient population.
2. While some recovery characteristics were faster following sevo, the differences from iso were not clinically important, and did not result in earlier readiness for discharge from the ambulatory unit. Furthermore, most or all of the faster recovery from sevo may have been due to the fact that the dose of sevo was significantly less. Because of the lower sevo dose, the sponsor cannot conclude from this study that sevo has better recovery characteristics than iso.

### STUDY 20: COMPARISON WITH PROPOFOL IN OUTPATIENTS

This study compared the anesthetic and recovery effects of sevoflurane and propofol in 283 ASA 1-2 patients undergoing surgical procedures as outpatients in 3 institutions in Europe and 4 in the US. The patients ranged in age from 18 to 75 (av 35) years, and were equally divided in gender. The most common operations were laparoscopy, knee arthroscopy and septoplasty. The mean duration of surgery was 54 min for the sevo patients and 60 min for the propofol patients. Anesthesia was induced in all patients with propofol 176 mg (range 60-700), and about half of the patients received fentanyl. The average sevo concentration was 0.6% (range 0.3-1.2), and the average propofol dose was 656 mg (range 89-2230). Nitrous oxide 60% was administered to both groups. About 40% of patients received fentanyl and vecuronium during maintenance of anesthesia.

#### Efficacy Assessment:

The times to emergence, response to commands, ability to walk without dizziness, and eligibility for discharge from hospital were significantly shorter for sevoflurane (8, 9, 153 and 364 min) than for propofol (10, 12, 176 and 472 min). Other times (extubation, orientation, eligibility for PAR discharge and ability to sit up without dizziness) were not significantly different. While the average time for walking without dizziness was significantly shorter for sevo, there were marked variations among investigators (4 of 7 had sevo shorter, and 3 of 7 found propofol shorter).

#### Safety Assessment:

The most often observed postoperative complication was cough, (37%), nausea (35%), and emergence secretions (19%). Bradycardia occurred in only 8% of sevo patients. There were no statistically different values for modified Aldrete score, pain discomfort, subjective feelings (visual analog scale), or psychomotor performance between the groups. Four patients in the sevo group developed more serious complications, ie: postop hypoxia, nausea and vomiting, urinary retention, and excessive bleeding. None of these seemed to be due primarily to sevoflurane administration, although it could have been a contributing factor. One patient in the sevo group developed a marked increase in SGOT postop (29 to 330 U/l), and two patients in the propofol group developed either an increase in SGOT (19 to 144 U/l) or creatinine (71 to

159 uM/).

**Conclusion:**

1. Sevoflurane produced anesthesia and recovery variables that were as favorable as those for propofol, except for the significantly higher incidence of nausea postoperatively.

**SUMMARY OF TWO STUDIES:**

From these two studies we can conclude:

1. Sevoflurane provides anesthetic conditions and recovery variables that are comparable to those for isoflurane or propofol in patients undergoing ambulatory surgical procedures.

2. The incidence of postoperative nausea would appear to be higher for sevoflurane than propofol.

Date: November 11, 1994

To: Bob Bedford, M.D.  
Acting Director, PDES

From: C. Philip Larson Jr., M.D. 

Subject: Sevoflurane Draft Label

The following are my recommendations regarding the Sevoflurane Draft Label.

1. Page 12: While the conclusion stated below the table on this page is true, without further information it is misleading. In most if not all of the studies cited in this table, the differences between sevoflurane and the reference drugs were:

- \* statistically significant but not clinically important
- \* due to the fact that the duration of exposure to sevoflurane was significantly shorter than the reference drug, the doses of the reference drug were not equipotent, or equipotency as in the case of propofol is not known.
- \* did not lead to significantly earlier discharge from the hospital or ambulatory service.

2. Page 14: In the section on Adult Anesthesia, the concluding statement is that sevoflurane is associated with shorter times for recovery events. Again this is misleading because the statement is true for some recovery events but not for others (ie: time to extubation, time to sitting without dizziness, time to discharge from hospital, etc. In the Ambulatory Surgery paragraph, while the ability to walk without dizziness was significantly shorter sevoflurane than propofol, the results were extremely variable among investigators (ie: 4 found sevoflurane better; 3 found propofol better).

3. Page 15: Again the table and conclusions are misleading because in the case of isoflurane the dose of sevoflurane was less; and in the case of propofol, there is no way to know whether equianalgesic doses were used.

4. Page 23: The paragraph on MH is misleading in that it does not state in direct terms that sevoflurane may trigger MH in susceptible patients. The fact that one case did occur in the clinical studies would dictate that it be made clearer that sevoflurane is a triggering agent for MH, and should not be used in susceptible patients.

5. Page 24: In the section on renal function, it should state that sevoflurane does cause higher levels of inorganic serum fluoride than the reference drugs, and that in some patients the level may exceed 50  $\mu\text{M}/\text{l}$ . Whether this proves to be of clinical importance will only be known as many more patients are exposed to the drug. There is at least one case in these clinical trials of a patient who developed renal insufficiency after exposure to sevoflurane. The clinician should know that infrequent renal insufficiency due to sevoflurane has not been ruled out.

6. Page 26: Sevoflurane is associated with a substantial incidence of nausea (40%) in most of the studies, and in some patients may be protracted. This should be stated. Severe bradycardia seems to occur in some patients as well, and perhaps deserves special mention.

## MEDICAL OFFICER REVIEW

**NDA#:** 20,478  
**NAME:** Sevorane (Sevoflurane)  
**SPONSOR:** Abbott Hospital Products  
One Abbott Park Road  
Abbott Park IL 60064-3500  
Phone (708) 937-3216  
**REVIEWER:** Robert G. Merin, M.D., Medical Officer  
**REVIEW DATE:** October 1994  
**SUBMISSION TYPE:** NDA  
**CSO:** Leslie Vaccari  
  
**RESUME:** Cardiovascular Studies: 26, 27, 28, 29

### Background

Studies 27 and 28 were pharmacologic studies using either human volunteers or healthy patients. References 26 and 29 were multicenter clinical studies investigating CABG patients (26) and patients at risk for CAD undergoing non-cardiac surgery (29).

### Pharmacologic Studies

#### Study 27:

**Design:** 21 healthy human volunteers were scheduled to receive 1.0, 1.5 and 2.0 MAC sevoflurane-O<sub>2</sub> (n=7); isoflurane-O<sub>2</sub> (n=7) or sevoflurane-N<sub>2</sub>O (n=7) in three phases; I.) controlled ventilation, II.) spontaneous ventilation, III.) controlled ventilation at the end of the experiments investigating only 1.0 and 2.0 MAC concentrations of the respective anesthetics.

State-of-the-art cardiovascular measurements were employed with arterial and thermal dilution pulmonary artery catheter; transthoracic (awake) and transesophageal (anesthetized) echo. Hemodynamic measurements included heart rate (HR), mean arterial pressure (MAP), cardiac output, central venous pressure (CVP), pulmonary artery pressures; mean (MPAP) and diastolic (PAD). Echo recordings included left ventricular end diastolic area (LVDA) and left ventricular end systolic area. Calculated hemodynamic indices included cardiac index (CI), stroke volume index (SVI), systemic vascular resistance (SVR). Echo calculations included systolic wall stress (SWS), left ventricular ejection fraction (LVEF), and velocity of circumferential fiber shortening (Vcfs). Statistical evaluation relied on one way analysis of variance and paired t-test.

## **Results**

A major problem with this study was the fact that one isoflurane volunteer was withdrawn before the study began so that the isoflurane n was only 6 to start with. Two volunteers did not complete the 1.5 MAC isoflurane and one more did not complete the 2.0 MAC isoflurane studies because of hypotension. Hence the numbers for statistical analysis of these higher concentrations of isoflurane are inadequate and any statistical comparison is invalid. In addition, the effects of 1 MAC isoflurane in this study are very different from those recorded for previous human volunteer studies. Consequently, I choose not to use the isoflurane data in this study for comparative purposes.

Body temperature and arterial blood gases were well controlled for both phases I and III of the study. The baseline demographics, arterial blood gases and hemodynamics were also comparable between the anesthetics except that MPAP and PVR were increased awake in the sevoflurane-oxygen group compared with the other groups.

### **I.) Controlled ventilation**

Sevoflurane produced marked and significant decreases in MAP at all doses versus awake.

The effect of 1.5 MAC was greater than 1.0 MAC.

Sevoflurane produced a mild but significant decrease in SVR at 2.0 MAC versus awake.

The decrease in SVR at 1.5 MAC was greater than 1.0 MAC.

There was no significant change in HR at any dose versus awake.

However, HR was higher at 1.5 MAC versus 1.0 MAC and at 2.0 MAC versus 1.0 MAC.

There was a moderate and significant decrease in CI at 1.0 MAC and 1.5 MAC.

There was a marked and significant decrease in SVI at all doses versus awake.

Sevoflurane decreased CVP, MPAP, PAD at 1.5 MAC versus awake.

Sevoflurane produced no change in LVEDA, LVEF, or LVcfs at any dose versus awake.

### **Comparison:**

Compared to previous human volunteer studies with isoflurane and desflurane, sevoflurane produced:

Less tachycardia than either isoflurane or desflurane.

More decrease in CI and SVI than isoflurane or desflurane at 1.0 and 1.5 MAC.

Less decrease in SVR than isoflurane or desflurane at all doses.

Note: the maximal desflurane dose in these studies was only 1.6 MAC.

II.) Spontaneous ventilation

	<u>AWAKE</u>	<u>TABLE</u>		
		<u>1.0</u>	<u>1.5</u>	<u>2.0 MAC</u>
pHa	7.42	7.35	7.31	7.24
PaCO <sub>2</sub>	39	46	51	65
PaO <sub>2</sub>	89	498	486	495

Differences from controlled ventilation:

More increase in HR.

More decrease in SVR.

No change in other measurements

Comparison:

Sevoflurane during spontaneous ventilation produced results very similar to both those seen with desflurane and isoflurane except: CI actually increased during spontaneous ventilation with both desflurane and isoflurane.

Likewise LVEF and Vcfs increased during spontaneous ventilation with desflurane. These differences suggest that either sevoflurane is more cardiodepressant or more SNS depressant than desflurane since the respiratory acidosis resulting from spontaneous ventilation produced less modification of the cardiodepressant effects of sevoflurane.

**Conclusion**

The isoflurane data in this study is questionable. Certainly the results at 1.5 and 2.0 MAC are not subject for statistical evaluation.

Sevoflurane is a dose related cardiac depressant.

The increased heart rate at 2.0 MAC partially counteracts this effect.

Sevoflurane appears to produce less tachycardia at 1.0 MAC than isoflurane and desflurane and less tachycardia at 2.0 MAC than desflurane.

Sevoflurane is a less potent systemic vasodilator than either desflurane or isoflurane.

Qualitatively however, the cardiovascular effects of desflurane, sevoflurane and isoflurane in human volunteers are similar except for the effects on heart rate.

Study 28:

Epinephrine induced arrhythmogenic effect of sevoflurane versus isoflurane in adult patients.

This study has been published in Anesthesiology (Navarro, et al 80:545-549, 1994.)

This is a repeat of previous studies by the same group with desflurane and isoflurane in patients for transsphenoidal hypophysectomy.

In these patients submucosal epinephrine in doses of 10, 13.3 or 20 mcg/ml were injected during 1.0-1.3 MAC sevoflurane or isoflurane.

**No ventricular arrhythmias were seen after epinephrine injection with either anesthetic at less than 5 mcg/kg doses of epinephrine. There was no differences between the anesthetics.**

**A previous study with desflurane versus isoflurane (Anesthesiology 79:943-947, 1993) indicated an epinephrine arrhythmic threshold of 7 mcg/kg for both anesthetics.**

#### **Conclusion**

**It is unlikely that there is a real difference in arrhythmogenic potential of epinephrine between the three anesthetics. The difference between the thresholds is undoubtedly due to individual variation. In addition, this is a less than quantitative study. For real accuracy, intravenous epinephrine should have been injected rather than submucosal.**

## Clinical Multicenter Studies

### Study 26:

#### Sevoflurane versus isoflurane in coronary artery bypass surgery.

This study was conducted in 13 centers in the US and 4 other countries. Patients were uncomplicated coronary artery bypass grafting candidates with good ventricular function, no recent myocardial infarction and stable angina.

Premedication and induction were standardized; the latter with midazolam (0.1-0.3 mg/kg) fentanyl (5-25 mcg/kg) and vecuronium (0.1-0.2 mg/kg).

One MAC sevoflurane (2.05%) or isoflurane (1.15%) were begun at a loss of consciousness.

The drugs were titrated throughout the pre-cardiopulmonary bypass period to a maximum of 2.0 MAC. Neither drug was administered during or after cardiopulmonary bypass.

Besides standard monitors, continuous two lead ST segment monitoring for 12 hours prior to anesthesia through the beginning of cardiopulmonary bypass was accomplished. The tapes were given a standard evaluation by a blinded cardiologist.

CPK-mB concentrations were measured every 8 hours for the first 3 postoperative day.

Standard definition of postoperative myocardial infarction was employed.

Ventricular failure was defined as a CI of  $< 2$  l/min/m<sup>2</sup> and or the use of an intra-aortic balloon pump. There was no mention of the use of inotropes incidence of pulmonary edema, etc.

Statistical Evaluation was adequate.

### Results:

140 patients were randomized to sevoflurane and 133 to isoflurane. Pre- and intraoperative demographics were comparable except that cross clamp and total cardiopulmonary bypass time were not documented. The average MAC dose was approximately 0.5 for both anesthetics. The mean MAC hours were 1.0 for sevoflurane and 0.92 for isoflurane.

All outcome data were entirely comparable including hemodynamics, use of cardioactive drugs, and ischemia incidence during anesthesia. There were no differences in postoperative incidence of myocardial infarction or ventricular failure as inadequately defined in the protocol.

It was curious that: 1.) there was an increase incidence of hypertension with sevoflurane in as much as concentration of sevoflurane should be more easily manipulated than isoflurane; 2.) there was a very low incidence of non-hemodynamically related ischemia; 3.) one sevoflurane patient (#1456) was described as having sevoflurane discontinued because of hypotension. Yet nowhere could I find the description of this patient.

### **Conclusion**

1. The n was barely adequate especially for a multicenter study.
2. The inhalation anesthetics were definitely used as supplements only prior to cardiopulmonary bypass.
3. The low incidence of continuous ST segment ischemia casts some doubt on the adequacy of monitoring or interpretation of this data.
4. As presented, there no significant differences in the conduct of anesthesia nor postoperative complications between sevoflurane and isoflurane in these relatively healthy coronary artery bypass graft patients.

### **Study 29:**

#### **Sevoflurane versus isoflurane in non-cardiac surgery in patients at risk for myocardial ischemia.**

This was a multicenter (13) multinational (3) study. All patients were New York Heart Association 1 (70%) or 2 (30%). Most patients did not have angina (72%).

The surgery was predominately cardiovascular (46%), GI (19%) and musculoskeletal (15%). There was a standardized diazepam premedication: induction was "consistent for each site" and utilized predominately thiopental, low dose fentanyl with or without vecuronium.

Anesthesia was initiated with approximately 1.5 MAC (sevoflurane 3%) (isoflurane 1.8%) supplemented with 50-70% nitrous oxide and titrated versus HR and BP. The continuous ST segment monitoring and criteria for postoperative myocardial infarction were the same as Study 26 except that the ST segment monitoring was continued for 48 hours postoperatively.

There were no cardiac output or filling pressure measurements reported.

The statistics were good.

## Results:

106 patients were randomized to sevoflurane and 108 to isoflurane. Pre- and intraoperative demographics were entirely comparable.

The average MAC doses for both anesthetics were 0.49! No documentation was provided as to what the rest of the anesthesia for these major surgical procedures consisted of. No dose for opiate agonists, intravenous hypnotics or even concentrations of nitrous oxide were provided.

It is of some interest that 99 and 100% of the sevoflurane and isoflurane patients respectively were noted to have received vecuronium yet only 56% received an anticholinesterase for reversal.

Only 83 in each anesthetic category were reported with continuous ST segment monitoring. Again, there was a very low incidence of non-hemodynamic related ST segment ischemia (although this was a much lower risk group than the coronary bypass patients).

There was no significant difference in the incidence of tachycardia, bradycardia, hypertension, hypotension or ischemia intraoperatively between the two groups. Likewise there was no difference in incidence of postoperative myocardial infarction. In addition, there was no difference in the other non-cardiac adverse events in the intraoperative or postoperative period.

## Problems:

1. The definition of the "at risk" patients. As noted, most of the patients were New York Heart Association class 1 and most had no clinical symptoms. Any patient with peripheral vascular disease or having peripheral vascular surgery was included as well as the patients with 3 risk factors including age > 65, hypertension, cholesterol > 240 mg/dl, diabetes mellitus, smoking history, so that in fact this was not a high risk group of patients.
2. For a multicenter study, especially considering the drop out for the ST segment monitorings I believe that the n is inadequate.
3. The anesthetic drugs need to be better defined. There were major surgical operations and the average dose of inhalation anesthetics was 0.5 MAC.
4. Again, there was a very low incidence of non-hemodynamically related ST segment ischemia contrary to reported results from patients with coronary artery disease.

### **Conclusion**

Within the limits of this study as indicated above, in patients at mild to moderate risk for myocardial ischemia undergoing relatively short surgery (mean duration 110 and 114 minutes) there was no difference at all in incidence of intra- and postoperative complications in well matched cohorts when sevoflurane and isoflurane were compared.

### **Labeling**

#### **Page 2:**

The significance of the interaction of sevoflurane with soda lime and baralyme is, to say the least, controversial. The labeling on Page 2 is not adequate. At the very least I believe that the agency should suggest in labeling that baralyme should not be used with sevoflurane. A new study published this year in Anesthesiology (Bito and Ikeda 80:71, 1994) documents in a clinical study the difference between the effect of baralyme and soda lime on the production of compound A.

#### **Page 8:**

The table needs to be totally redone. I would prefer that the isoflurane segment be totally eliminated but at the very least the 1.5 and 2.0 MAC segments need to be eliminated because of the low n and the lack of validity of statistical evaluation (see the medical officer summary).

There needs to be a summary statement which should be similar to my summary in the medical officer summary such as:

**Sevoflurane in human volunteers is a dose related cardiac depressant.**

**In contrast to previously reported studies with desflurane and isoflurane, heart rate increases only at 2.0 MAC doses of sevoflurane, so that at lower and more clinically applicable doses, sevoflurane produces less tachycardia than isoflurane or desflurane. On the other hand, cardiac output is decreased even at 1.0 MAC in contrast to both sevoflurane and desflurane and as a result of the dose related decrease in mean arterial pressure, sevoflurane is a less potent systemic vasodilator than either desflurane or isoflurane.**

**A study investigating the epinephrine induced arrhythmogenic effect of sevoflurane versus isoflurane in adult patient undergoing transsphenoidal hypophysectomy demonstrated that the threshold dose of epinephrine producing multiple ventricular arrhythmias was 5 mcg/kg with both sevoflurane and isoflurane. Consequently it seems that, the interaction of sevoflurane with epinephrine is equivalent to that seen with isoflurane.**

**Cardiovascular Surgery: Coronary Artery Bypass Grafting:**

I believe this section should be markedly changed as follows:

Sevoflurane was compared to isoflurane as an adjunct with narcotics in a multicenter study of 273 patients undergoing CAB surgery. Anesthesia was induced with midazolam 0.5-0.3 mg/kg; vecuronium 0.1-0.2 mg/kg and fentanyl 5-15 mcg/kg. Both isoflurane and sevoflurane were administered at loss of consciousness in doses of 1.0 MAC and titrated until the beginning of cardiopulmonary bypass to a maximum of 2.0 MAC. The total dose of fentanyl did not exceed 25 mcg/kg. The average MAC dose was 0.49 for sevoflurane and 0.53 for isoflurane. There were no significant differences in hemodynamics, cardioactive drug use or ischemia incidence between the two groups. Outcome was also equivalent. In this small multicenter study, it would appear that sevoflurane is as effective and as safe as isoflurane for supplementation of opioid anesthesia for coronary bypass grafting.

**Non-cardiac Surgery in Patients at Risk for Myocardial Ischemia:**

More information is necessary for labeling as indicated in the medical officers review of Study 29. Assuming that this information is satisfactory, I would amend the labeling as follows:

Sevoflurane-nitrous oxide was compared to isoflurane-nitrous oxide for maintenance of anesthesia in a multicenter study in 214 patients, age 40-87 years, who were at mild to moderate risk for myocardial ischemias and were undergoing elective non-cardiac surgery. 46% of the operations were cardiovascular with the remainder evenly divided between gastrointestinal and musculoskeletal and small numbers of other surgical procedures. The average duration of surgery was less than 2 hours. Anesthesia induction was performed usually with thiopental (2-5 mg/kg) and fentanyl (1-5 mcg/kg). Vecuronium (0.1-0.2 mg/kg) was also administered either to facilitate intubation, muscular relaxation or immobility during surgery. Either sevoflurane or isoflurane was administered at loss of consciousness in 1.5 MAC doses which were then titrated through the rest of the procedure. The average MAC dose was 0.49 for both anesthetics. There was no significant difference between the anesthetic regimens, for intraoperative hemodynamics, cardioactive drug use or ischemia incidents, although only 83 patients in each category were successfully monitored for ischemia. The outcome was also equivalent in terms of adverse events, death and postoperative myocardial infarction. Within the limits of this small multicenter study in patients at mild to moderate risk for myocardial ischemia, sevoflurane was a satisfactory equivalent to isoflurane in providing supplemental inhalation anesthesia to intravenous drugs.

**MEDICAL OFFICER REVIEW**

**NDA #:** 20,478  
**NAME:** Sevoflurane (Sevoflurane)  
**SPONSOR:** Abbott Hospital Products  
One Abbott Park Road  
Abbott Park IL 60064-3500  
Phone (708) 937-3216  
**REVIEWER:** Robert G. Merin, M.D., Medical Officer  
**REVIEW DATE:** November 4, 1994  
**SUBMISSION TYPE:** NDA  
**CSO:** Leslie Vaccari  
  
**RESUME:** Cardiovascular Studies: 42



**Background**

Both isoflurane and desflurane stimulate the sympathetic nervous system (SNS) transiently upon rapid increase in inspired concentrations both during induction and steady state anesthesia producing significant tachycardia and hypertension (1-3). The same laboratory that discovered this effect for desflurane has now studied sevoflurane.

**Pharmacologic Studies**

Design: 10 male volunteers were instrumented with:  
intravenous and radial artery catheters  
peroneal nerve electrodes at the right fibular head for recording of SNS peripheral nerve traffic  
forearm vascular resistance by strain-gauge plethysmograph  
arterial epinephrine and norepinephrine concentrations  
baroreceptor stress testing using hypotension with sodium nitroprusside and hypertension with phenylephrine.

Protocol: Anesthetic induction was accomplished with 2-3 mg/kg propofol. Mask oxygen (30%), air and sevoflurane (1%-1 min., 2%-1 min., 3%) until endotracheal intubation (ETI).

Vecuronium for neuromuscular blockade.

After 10-12 minutes, ETI.

Sevoflurane concentration was:

Decreased to 1% for 30 minutes.

- Increased to 2% with q 1 minute measurements maintained at 2% for 15 minutes.

Increased to 3% with q 1 minute measurements maintained at 3% for 15 minutes.

All measures except for baroreceptor stress testing were recorded during induction and change of sevoflurane concentrations during maintenance. Baroreflex stress testing was done at only awake and steady state end-tidal concentrations.

### **Statistics**

There was inadequate description of statistics (Full Summary-Page 15). Appendix C. (named a Statistical Evaluation) recorded only mean, standard error, minimum and maximum values for the recorded variables.

### **Results**

From graphs, Full Summary Page 22-31 and tables, Appendix C. Page 192-211.

- Note:
1. As indicated before, there was inadequate presentation of statistics.
  2. Appendix C. Page 220-223 lists tabular data for central venous pressure recording. There is no mention of a central venous pressure catheter in the complete summary. Justification for this catheter and route of insertion need to be documented.

Induction: There was a gradual reduction in mean arterial pressure; a small increase in heart rate; a marked decrease in muscle SNS activity (MSNA) and a marked decrease in forearm vascular resistance (FVR). Most of these effects were probably related to the propofol induction.

Sevoflurane: With the introduction of sevoflurane during induction, there was continued decrease in mean arterial pressure and forearm vascular resistance with no change in heart rate or MSNA (? statistical significance [SS]).

Mean arterial pressure, heart rate, MSNA and forearm vascular resistance all increased markedly with endotracheal intubation (? SS).

Steady state Sevoflurane: Heart rate was back to baseline at 1% sevoflurane and increased slightly at steady state 2% and 3% sevoflurane (? SS).

Mean arterial pressure returned to baseline at 1% sevoflurane and was decreased at 2 and 3% (? SS).

MSNA did not return to either baseline (decreased) or the level after propofol induction (increased). There was no change with increasing concentrations of sevoflurane.

FVR was decreased at 1% sevoflurane and further decreased at 2 and 3% sevoflurane (? SS).

Plasma nor epinephrine was decreased at 1% sevoflurane and returned to baseline at 2 and 3% sevoflurane. There was no change in plasma epinephrine although there were many missing values.

Peripheral baroreflex slope (MSNA) was markedly and dose dependently decreased by sevoflurane (? SS).

Cardiac baroreceptor slope (? heart rate) was markedly and dose dependently depressed by sevoflurane during hypotension (? SS).

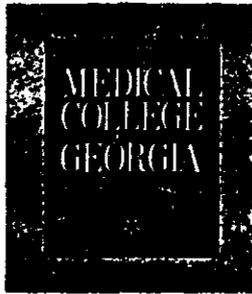
Cardiac baroreceptor slope was unchanged until 3% sevoflurane during hypertension.

### **Discussion**

The discussion on Page 41 of the Full Summary is generally accurate. However, the conclusion needs to be modified because, in fact as indicated above there was marked decrease in baroreceptor function with hypotension both as evaluated by MSNA and heart rate response. It is true that during hypertension baroreflex response was preserved until 3% (1.5 MAC) sevoflurane. The general results and conclusions of this study suggest that unlike desflurane and isoflurane, sevoflurane is not associated with any SNS activation either during induction or increased inspired concentrations during steady state. In addition, this study suggests that sevoflurane produces significant sympathetic nervous system depression that appears to be dose related.

## References

1. Helman, et al: Comparison of Desflurane and Sufentanil in Patients Undergoing Coronary Artery Surgery. *Anesthesiology* 77:47-62, 1992.
2. Ebert and Muzi: Sympathetic Hyperactivity During Desflurane Anesthesia in Healthy Volunteers: A Comparison with Isoflurane. *Anesthesiology* 79:444-453, 1993.
3. Weiskopf et al: Rapid Increase in Desflurane Concentration is Associated with Greater Transient Cardiovascular Stimulation than with Rapid Increase in Isoflurane Concentration in Humans. *Anesthesiology* 80:1035-1045, 1994.



ORIGINAL

School of Medicine  
Department of Anesthesiology

November 8, 1994



Robert Bedford, M.D.  
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L NEW CORRESP  
C

Dear Dr. ~~Bedford~~, <sup>Merin</sup>

I received data for this study from Abbott last week. I believe the results should be incorporated in the NDA Review. Consequently I am forwarding my revision of that study.

Sincerely,

Robert G. Merin, M.D.  
Professor of Anesthesiology

sfg

**REVIEW: FDA**

NDA# 20-478  
NAME: Sevoflurane (Sevoflurane)

Reviewer: Margaret Wood, MD  
Review Date: October/November, 1994

Resume: Pediatric Studies #1,21,22,23,24,25

**Background**

Sevoflurane was evaluated in two pivotal studies and four supporting studies in pediatric patients undergoing various types of surgical procedures. In Study #1, sevoflurane alone was evaluated, while in Study #21, halothane was used as the comparative anesthetic.

**Study 1: MAC of Sevoflurane in Pediatric Patients.**

90 patients 0 - 10 years old (ASA I, II) undergoing surgical procedures of less than 60 minutes duration received sevoflurane in O<sub>2</sub> or sevoflurane in 60% N<sub>2</sub>O/40% O<sub>2</sub> administered through an Ayres T piece, so no interaction with soda lime was possible. MAC was determined by using the response to incision as the stimulus and the "up and down" method of Dixon." The MAC values determined for sevoflurane in oxygen (O<sub>2</sub>) in pediatric patients were:

3.26% in 0 - <1 month, 3.01% in 1 - <6 months, 2.80% in 6 - <12 months, 2.65 in 1 - <3 years, 2.53% in 3 - <5 years and 2.41% in 5-12 years. The MAC values for sevoflurane in N<sub>2</sub>O/O<sub>2</sub> was 1.98% in 1 - 3 years age group.

Efficacy Assessment

Mean induction time for 78 patients was 1.1 ± 0.0 min (range 1-3 min). MAC exposure varied from 0.4 to 3.6 hours for all patients. Mean time to emergence was 12.3 ± 0.9 min.

Safety Assessment

Most common adverse experiences included somnolence (28%) and vomiting (16%). C<sub>max</sub> (max observed concentration) for fluoride ranged from 1.5 to 27.0 μM. One patient had post discharge bleeding (not considered to be related to the anesthetic) and another experienced post extubation apnea prior to emergence. None of the laboratory values were considered to be abnormal.

**Study 21: Induction and Maintenance of Anesthesia: Sevoflurane vs Halothane**

525 patients ASA I, II were studied as part of a multicenter randomized open label study comparing sevoflurane to halothane in pediatric patients. Ratio of halothane to sevoflurane was 1:1. Anesthesia exposure was 1.10 ± 0.03 MAC hours for sevoflurane and 1.27 ± 0.03 MAC hrs for halothane. It is not clear in the Methods section as to type of anesthetic circuit and flow rates used.

### Efficacy Assessment

Induction times were  $1.7 \pm 0.06$  and  $2.2 \pm 0.06$  min for sevoflurane and halothane respectively ( $p < 0.001$ ); while emergence was more rapid for sevoflurane than halothane ( $11.9 \pm 0.59$  vs  $19.4 \text{ mins} \pm 0.59$   $p < 0.001$ ). The most common adverse experience was agitation, 31% in the sevoflurane group and 18% in the halothane group. 21% of patients in both groups received vecuronium, while there was no significant difference in fentanyl dose between the two groups. Sevoflurane patients had significantly higher objective pain discomfort scores than halothane patients in the first 40 minutes post-anesthesia, which may be related to postoperative restlessness.

### Safety Assessment

There was no significant difference for overall cardiovascular parameters between the two groups, but eight patients in the halothane group as opposed to one patient in the sevoflurane group experienced bradycardia. The incidence of agitation was higher in the sevoflurane group than the halothane group of patients. Seven patients in the sevoflurane group and two in the halothane group experienced severe adverse experiences. In the sevoflurane group two patients experienced apnea and one patient laryngospasm. In the halothane group, one patient exhibited drowsiness/somnolence.

No fluoride or Compound A estimations were carried out as part of the safety assessment of sevoflurane in this study. None of the laboratory values were considered by the investigators to be clinically significantly abnormal. Two halothane outliers were reported for SGPT/ALT.

### **Study 22: Induction and Maintenance of Anesthesia: Sevoflurane vs Halothane in Pediatrics**

Sevoflurane was compared to halothane anesthesia in 50 pediatric (ASA I, II) patients, as part of an open label randomized study in which the ratio of sevoflurane to halothane patients was 1:1. Anesthesia exposure was  $2.44 \pm 0.254$  MAC hours for sevoflurane and  $3.06 \pm 0.254$  MAC hours for halothane. Vecuronium and fentanyl were given as clinically indicated.

### Efficacy Assessment

Patients were induced and emerged in  $1.0 \pm 0.09$  minutes and  $17.1 \pm 3.05$  minutes with sevoflurane compared to  $1.7 \pm 0.09$  minutes and  $35.4 \pm 3.05$  minutes with halothane ( $p < 0.001$ ). Time to response to commands, orientation and first analgesia was significantly faster in the sevoflurane group than the halothane group. The modified Trieger dot test score at 1 and 2 hour post anesthesia was only statistically different at 1 hour post-anesthesia.

### Safety Assessment

The maximum fluoride concentrations ( $C_{max}$ ) ranged from 14.0 to 45.00  $\mu\text{M}$ , with a peak concentration occurring at approximately 1.4 hours. No serious adverse experiences were reported, and there were no significant differences between halothane and sevoflurane study patients for adverse effects. In one sevoflurane patient, BUN was increased to 21 mmol/L on Day 2. In one halothane patient, a clinically significant abnormal value for WBC was reported.

### **Study 23: Induction and Maintenance of Anesthesia: Sevoflurane vs Halothane in Pediatric Patients**

This was a multi center (12 sites) randomized study comparing sevoflurane to halothane in 428 pediatric patients (ASA I, II) 1 month - 18 years of age. Sevoflurane patients were induced in  $2.1 \pm 0.28$  minutes compared to  $2.9 \pm 0.26$  minutes in halothane patients, while emergence was  $10.3 \pm 0.87$  minutes for sevoflurane and  $13.9 \pm 0.80$  minutes for halothane patients. Vecuronium and fentanyl were administered if clinically indicated.

#### Efficacy Assessment

Sevoflurane produced a slightly faster induction than did halothane; similarly for emergence (see above). Anesthesia exposure was  $2.15 \pm 0.115$  MAC hours for sevoflurane and  $2.22 \pm 0.106$  MAC hours for halothane (NS). Time to orientation, first analgesia and eligibility for discharge from recovery revealed no significant differences between groups. However, objective pain discomfort scale total scores were significantly higher for the sevoflurane patients for 20 minutes post-anesthesia. VAS scores were essentially similar for both groups during the post-anesthesia period (up to 120 minutes).

#### Safety Assessment

$C_{max}$  for fluoride concentration ranged from 7.1 to 34.2  $\mu\text{M}$ . The most common adverse experience was vomiting, 31% in sevoflurane patients and 40% for halothane patients (NS). 2% of sevoflurane patients exhibited bradycardia compared to 12% of halothane patients ( $p < 0.001$ ). Five patients in the sevoflurane group were reported as having serious adverse experiences; but none appeared to be related to the study drug. In the halothane group, 7 patients experienced serious adverse experiences; 1 patient developed malignant hyperthermia. The other adverse experiences appeared to be unrelated to the study drug. Four sevoflurane and 4 halothane patients had clinically significant abnormal BUN values, while 2 sevoflurane patients had abnormal creatinine levels. One halothane and 1 sevoflurane patient had abnormal SGOT/AST levels.

### **Study 24: Induction and Maintenance: Sevoflurane vs Halothane in Pediatric Patients**

120 patients (2 sites) were randomized to receive sevoflurane/ $\text{O}_2$ , sevoflurane/ $\text{N}_2\text{O}/\text{O}_2$  or halothane/ $\text{N}_2\text{O}/\text{O}_2$  = ratio being 1:1:1. Anesthesia exposure was  $3.57 \pm 0.267$  MAC hours for sevo/ $\text{O}_2$ ;  $3.09 \pm 0.267$  for sevo/ $\text{N}_2\text{O}/\text{O}_2$  and  $2.82 \pm 0.267$  for halothane/ $\text{N}_2\text{O}/\text{O}_2$ .

#### Efficacy Assessment

Patients were induced in 1.7, 1.6 and 1.9 minutes with sevo/ $\text{O}_2$ , sevo/ $\text{N}_2\text{O}/\text{O}_2$  and Hal/ $\text{N}_2\text{O}/\text{O}_2$  respectively, while emergence times were 12.5, 15.5, and 25.7 minutes following sevo/ $\text{O}_2$ , sevo/ $\text{N}_2\text{O}/\text{O}_2$  and hal/ $\text{N}_2\text{O}/\text{O}_2$ . The most common adverse experience was vomiting, but there was no statistical significance between the groups.

#### Safety Assessment

Fluoride  $C_{max}$  for sevo/ $\text{O}_2$  was 16.04 and for sevo/ $\text{N}_2\text{O}/\text{O}_2$  was 15.51  $\mu\text{M}$ . No range was reported. However, it is important to investigate the "outliers" in regard to possible fluoride induced toxicity. Two patients in the sevoflurane group experienced serious adverse effects,

but none were related to the study drug. None of the patients in Study 24 had laboratory values considered to be clinically significantly abnormal.

### **Study 25: Induction and Maintenance: Sevoflurane vs Halothane in Pediatric Patients**

375 patients (ASA I, II) were randomized to receive sevoflurane /N<sub>2</sub>O or halothane/N<sub>2</sub>O for induction and maintenance of anesthesia. Ratio of sevoflurane to halothane patients studied was 2:1. Anesthesia exposure time was 1.09 MAC hours for sevoflurane and 1.24 MAC hours for halothane.

#### Efficacy Assessment

Sevoflurane induction was faster than halothane induction ( $1.3 \pm 0.0$  vs  $1.6 \pm 0.1$   $p < 0.001$ ) and similarly for emergence ( $11.3 \pm 0.7$  vs  $19.4 \pm 1.0$   $p < 0.001$ ).

#### Safety Assessment

Again the most common adverse effect was vomiting, 22% for sevoflurane and 35% for halothane,  $p = 0.006$ . The objective pain discomfort score was significantly higher for sevoflurane patients than halothane patients for the first 30 minutes post-anesthesia. Agitation was increased in sevoflurane patients compared to halothane patients. One sevoflurane patient had a serious adverse experience - apnea, which was probably related to the study drug. One halothane patient experienced airway obstruction and hypoxia, considered to be a serious adverse effect. No fluoride concentrations were measured. No clinically significant abnormal laboratory values were reported.

## **CONCLUSIONS FROM STUDIES**

Abnormal chemistry (liver/kidney) occurred in a few patients. No studies were performed using more sophisticated methods of investigation of renal function. In view of some relatively high fluoride concentrations, this may be required if sevoflurane is to be considered for more prolonged administration in pediatric patients. In addition, no mention was made of gas flow/circuit type which may be of importance for possible compound A production. Future studies regarding preoperative drug therapy and fluoride production may be required, e.g. inducers of CYP2E1.

The Pediatric Studies demonstrate that sevoflurane may produce a faster induction and more rapid emergence and recovery. Restlessness/agitation may be more common after sevoflurane than halothane, possibly due to discomfort from surgery.

## **RECOMMENDATIONS REGARDING LABELING**

### Label Changes - Pediatric anesthesia section

First paragraph is satisfactory

Second Paragraph - Mask Induction

This paragraph gives statistical significance for time for mask induction, but does not give the actual times. This is then repeated with the induction times but without significance in the ambulatory section. The induction times and significance values should be given together as one statement in only one of the paragraphs. I presume that the second paragraph relates to the pivotal study 21 - Induction and Maintenance of Anesthesia: Sevoflurane vs Halothane in Pediatric Patients. The induction time was significantly shorter  $p < 0.001$   $1.7 \pm 0.6$  vs  $2.2 \pm 0.06$  mins, see next paragraph. I think that they should give the actual induction time here with the significance values. Secondly the incidence of coughing was stated to be statistically lower for sevoflurane than with halothane ( $p = 0.003$ ). However, on my perusal it looked as though there was no statistical significance for coughing - Table 14, page 13. Which studies were they referring to for their statement  $p = 0.003$ ? I think that they should give the actual incidence of coughing as compared with halothane. From other studies/reviews, it does appear that coughing, breath-holding and laryngospasm may be unusual with sevoflurane administration.

**Third Paragraph - Ambulatory surgery**  
Relates to 525 patients - study 21.

No mention is made of increased agitation with sevoflurane.

Sevoflurane (max 7%) etc . . . Sentence does not read correctly -- verb is missing.

I would like to comment on some aspects of the label that were not assigned to me:

1. Page 2 - last paragraph  
Cytochrome P450 2E1, thus far, is the only . . .
2. CYP 2E1 is not induced by barbiturates, but is induced by ethanol and isoniazid, and therefore these drugs have the potential to induce sevoflurane metabolism. This may need to be considered for the drug interaction section.
3. Should the fluoride concentrations achieved in the pediatric patients for a stated number of MAC hours of sevoflurane anesthesia be given in the Pediatric section or in any other section? They were measured in many of the studies. It is also important to give the range of fluoride concentrations (as was done in the summary) rather than merely mean concentrations.

MEDICAL REVIEW

NDA#: 20,478  
NAME: Sevorane (Sevoflurane)  
SPONSOR: Abbott Hospital Products  
One Abbott Park Road  
Abbott Park, IL 60064-3500  
Phone (708) 937-3216  
REVIEWER: Marie L. Young, M.D. , ALSAC member  
REVIEW DATE: September 1994  
SUBMIS. TYPE: NDA  
CSO: Leslie Vaccari



**RESUME: Renal, Hepatic, Elderly Studies**

**Background:**

Sevoflurane was evaluated for effects on renal function, hepatic function and the elderly in six studies. Two studies addressed renal concentrating ability in healthy volunteers (#30, 35), two studies addressed renal effects in patients with renal compromise (#31, 34), one study compared sevoflurane to isoflurane in the elderly (#32), and one study compared sevoflurane to isoflurane in hepatically impaired inpatients (#33). Table 1 summarizes the parameters measured in each study.

Table 1.

Measurement Parameters	Study #					
	30 *	35	31 *	34	32	33
<b>Efficacy assessment:</b>						
renal function						
renal concentrating ability (urine osmolality)	x	x				
serum creatinine and/or creatinine clearance	x	x	x	x		x
BUN, urine specific gravity	x		x			
time to recovery events	x		x		x	
clinical evaluation success rates	x			x	x	
recovery parameters						
VAS: Visual Analog Scale	x				x	
DSST: Digit Symbol Substitution Test	x				x	
Modified Aldrete Score	x				x	
OPDS: Objective Pain-Discomfort Scale					x	
intraoperative recall	x			x	x	
<b>Safety Assessment:</b>						
serum inorganic fluoride measurements						
Cmax: maximum observed fluoride concentration ( $\mu\text{M}$ )	x	x	x	x	x	x
Tmax; time of maximum observed fluoride concentration (min)	x	x				x
AUC; area under the fluoride concentration versus time curve ( $\mu\text{M}/\text{min}$ )	x	x				x
clinical lab data (hematology, blood chemistry, urinalysis)	x	x	x			x
pre/postop LFTs	x	x	x	x	x	x
adverse experience monitoring	x	x	x	x	x	x
physical assessment	x	x	x			x

\* = pivotal study

## Clinical Studies

### Study 30 (pivotal)

This single center, open label randomized study of 28 healthy male volunteers ages 21-35 years (Tucson, AR) compared 7 subjects receiving 3.0 MAC-hours sevoflurane O<sub>2</sub>/air to 7 receiving enflurane O<sub>2</sub>/air, then 7 subjects receiving 9.6 MAC hours sevoflurane O<sub>2</sub>/air to 7 receiving enflurane O<sub>2</sub>/air to assess renal concentrating ability with prolonged anesthesia exposure. Subjects received propofol 1-2 mg/kg for induction and d-tubocurarine (3 mg) plus succinylcholine 1-2 mg/kg for intubation.

A semi-closed circuit system containing soda lime was used; maintenance gas flows were not specified. The planned number of enrollees (28) was achieved.

### **Efficacy Assessment:**

Sevoflurane did not produce any defect in renal concentrating ability determined by desmopressin acetate (DDAVP) administration and fluid restriction pre-study, 1 day post-anesthesia and 5 days post-anesthesia. In the 9.6 MAC-hour group, 2/7 enflurane subjects had maximal urine osmolality values < 800 mOsm/kg; the lowest maximal urine osmolality value for sevoflurane was 864 mOsm/kg. The decrease in urine osmolality was greater in the 3.0 MAC-hour than the 9.3 MAC-hour group, presumably due to shorter collection times. Renal function was not affected as measured by BUN, creatinine and urine specific gravity.

Clinical evaluation success rates and emergence success were comparable between groups at 3.0 and 9.6 MAC-hours. Sevoflurane subjects had faster recovery than enflurane with some measures and better recovery characteristics, especially with shorter exposure. They had shorter emergence times, performed better than enflurane subjects at DSSTs and had better modified Aldrete scores at 3.0 and 9.6 MAC-hours. Ability to sit up, walk and discharge eligibility were comparable between groups at 9.6 MAC-hours. Average MAC-hour exposure was slightly but statistically significantly less in both sevoflurane groups. Differences were clinically different at 3 MAC-hours but not 9.6 MAC-hours.

No subjects had any recall of "intraoperative" events when questioned at recovery and at 24 hours post-anesthesia.

### **Safety Assessment:**

Fluoride levels exceeded 50  $\mu\text{M}/\text{L}$  in 3/14 sevoflurane subjects on the day of anesthetic exposure. None of the 14 enflurane subjects had inorganic plasma fluoride concentrations  $\geq 50 \mu\text{M}$ . The mean C<sub>max</sub> and highest single value for fluoride concentrations in the 7 sevoflurane subjects were 48.4  $\mu\text{M}$  and 63.2  $\mu\text{M}$ , respectively. Despite production of higher inorganic fluoride levels than enflurane, sevoflurane had less impact on urine concentrating ability as measured by C<sub>max</sub>, T<sub>max</sub> and AUC. These elevated concentrations were transient, substantially reduced 24 hours post-anesthesia and not associated with an effect on renal function.

One enflurane subject experienced elevated SGOT/AST on Day 1 post-anesthesia

which had returned to normal by Day 5 post-anesthesia. One sevoflurane and 1 enflurane subject each had slightly elevated SGOT/ASTs which were not considered to be clinically significant by the investigator. Adverse experiences were mild-to-moderate; no serious adverse experiences were reported. No subjects withdrew from the study due to adverse experiences. The most common reported adverse experiences were:

nausea:	3/7 sevoflurane subjects at 3.0 and 9.6 MAC-hours
	6/7 enflurane subjects at 3.0 and 9.6 MAC-hours
headache:	4/7 sevoflurane subjects at 3.0 MAC-hours
	5/7 enflurane subjects at 3.0 MAC-hours
vomiting:	3/7 sevoflurane subjects at 9.6 MAC-hours
	6/7 enflurane subjects at 9.6 MAC-hours

These differences were not statistically significant, but the n's were small.

### Study 35 (supportive)

This single center, open-label randomized study (U.K.) in healthy male volunteers ages 18-35 compared sevoflurane O<sub>2</sub>/air to enflurane O<sub>2</sub>/air (mask induction, vecuronium) in concentrations up to 1.3 MAC for effects of prolonged exposure on renal concentrating ability following 6 MAC-hours (n=6 sevoflurane, 6 enflurane subjects) or 9 MAC-hours anesthesia (n=5 sevoflurane, 5 enflurane subjects). In addition, serum inorganic fluoride levels were measured prior to, during and up to 6 hours following anesthesia.

A noncomparative first phase studied 5 subjects exposed to 3 MAC-hours of sevoflurane, then 5 additional subjects exposed to 6 MAC-hours of sevoflurane. The comparative study between sevoflurane and enflurane followed. Twelve subjects received 6 MAC-hours of sevoflurane or enflurane anesthesia; another 10 subjects received 9 MAC-hours of sevoflurane or enflurane anesthesia. Average MAC exposure was comparable between the 6 MAC-hour groups; in the 9 MAC-hour group, average MAC exposure was slightly less in the enflurane group.

Maintenance gas flows were not specified.

### Efficacy Assessment:

Urine concentrating ability (osmolality) was evaluated following 18 hours of fluid restriction and creatinine clearance. In the 9 MAC-hour group, 1 sevoflurane subject had a urine osmolality of 654 mOsm/kg on day 3 post-anesthesia, which increased to 1019 mOsm/kg on day 5 post-anesthesia. No other urine concentrating defect was observed.

Urine osmolality values at 6 MAC-hours and 9 MAC-hours:

on day 1 post-anesthesia were comparable for sevoflurane (6) and enflurane (6).

on day 3 post-anesthesia were comparable for sevoflurane (6) and enflurane (6).

Later measurement points are difficult to interpret because of the loss of subject measurement data with increasing time post-anesthesia.

Creatinine clearance values were comparable between sevoflurane and enflurane.

### **Safety Assessment:**

Serum inorganic fluoride peak values were measured at 8.2-16 hours for 6 and 9 MAC-hours exposure. Mean C<sub>max</sub> at 3, 6 and 9 MAC-hour anesthesia exposure were comparable. Mean AUC by dose at 3, 6 and 9 MAC-hour was  $184 \pm 65$ sd,  $134 \pm 31$ sd and  $101 \pm 14$ sd, respectively. No subject had serum inorganic fluoride concentrations  $\geq 50$   $\mu$ M at any measurement point.

The most commonly reported adverse experiences in the comparison groups involved the nervous system (agitation in 5/6 sevoflurane and 4/6 enflurane subjects) in the 6.0 MAC-hour group and the digestive system (vomiting in 1/5 sevoflurane and 5/5 enflurane subjects) in the 9.0 MAC-hour group.

One of 21 sevoflurane patients experienced elevated SGPT/ALT ( $>45$  U/L) postoperatively.

### **Study 31 (pivotal)**

This multicenter (3 sites - France, Germany, Belgium), randomized, open-label study of 41 inpatients (21 sevoflurane, 20 enflurane), ASA PS II-III, ages 29-83 with renal compromise (baseline serum creatinine  $\pm 1.5$  mg/dL) compared the effect on laboratory parameters of sevoflurane N<sub>2</sub>O/O<sub>2</sub> to enflurane N<sub>2</sub>O/O<sub>2</sub> anesthesia of up to 3 hours duration in renal compromised inpatients. Patients underwent intravenous induction and received various other anesthetic agents for supplementation. Average MAC-hours and MAC exposure were comparable between groups.

A rebreathing circuit was used; maintenance gas flows were not specified. The estimated sample size (40) was attained.

### **Efficacy Assessment:**

Serum creatinine, BUN, hemoglobin, hematocrit, sodium or potassium were measured in both groups at the end of anesthesia, and 48 and 72 hours post-anesthesia.

Sevoflurane was comparable to enflurane for anesthetic maintenance and recovery parameters in renal compromised adults. Mean times to response to commands were statistically shorter with sevoflurane. Neither drug caused further impairment of renal function as determined by pre and postoperative values for serum creatinine.

### **Safety Assessment:**

One sevoflurane patient had serum inorganic fluoride concentration  $\geq 50$   $\mu$ M (51.8  $\mu$ M) on the day of anesthetic exposure. The majority of patients in both groups reached peak inorganic fluoride concentrations at the end of anesthesia.

Pre and post anesthesia values for hemoglobin, hematocrit, creatinine, BUN, sodium and potassium were comparable between groups. However, 1 enflurane patient experienced elevation in BUN from 30.2 mmol/L to 70.3 mmol/L on post-anesthesia day 10.

Pre and postoperative values for SGOT/AST, SGPT/ALT and serum creatinine were not significantly different. One sevoflurane patient experienced elevation in SGOT/AST from 10  $\rightarrow$  56 U/L and elevation in SGPT/ALT from 7  $\rightarrow$  71 U/L; follow-up values on post-anesthesia day 12 were normal.

Adverse experiences were mild or moderate, and they were comparable between groups. The most commonly reported adverse experience was hypotension in 11/21 sevoflurane patients and 10/20 enflurane patients. There were no withdrawals from the study due to adverse experiences. Two sevoflurane patients had possibly study drug-related experiences; ↑ed SGPT/ALT and SGOT/AST in 1 patient, and ↑ed BUN, creatinine in another patient.

Three sevoflurane patients had serious adverse experiences, none of which were considered related to sevoflurane exposure. One PS III patient died on postoperative day 7; the most likely cause of death was pulmonary embolism and pneumonia. Another PS III patient died on tenth day post sevoflurane exposure following attempted repeat peripheral vascular surgery, left AKA under isoflurane anesthesia, and subsequent severe cerebrovascular accident. A third PS III patient experienced postoperative fever. One PS III patient who received enflurane had a serious adverse experience, i.e., deterioration in renal function 72 hours postoperatively; his renal function was stabilized, but he left the hospital before the etiology of renal dysfunction could be determined.

#### **Study 34 (supportive)**

This multicenter (4 sites - U.S.), randomized, open-label study compared sevoflurane/O<sub>2</sub> (n=14) to isoflurane/O<sub>2</sub> (n=12) administration in patients with renal insufficiency (serum creatinine of 132.6-265.2 μmol/L) during operations lasting 1-6 hours. Propofol 2.0 mg/kg was administered for induction, and patients received various other anesthetic agents during maintenance. Most patients received vecuronium, fentanyl, neostigmine and glycopyrrolate. MAC-hours and average MAC exposure were comparable between groups.

Only 1 patient was enrolled at the Miami site; this patient was excluded from statistical analyses evaluating investigator effects, duration of surgery or anesthetic administration, and times to anesthesia and recovery events.

Anesthetics were administered via a rebreathing circuit; maintenance gas flows were 5 L/min. The study design anticipated 40 enrollees; 26 were obtained.

#### **Efficacy Assessment:**

Renal function as assessed by serum creatinine, creatinine clearance pre and 24 hours post-anesthesia (also at 48 and 72 hours post-anesthesia if the patient remained hospitalized) was essentially unchanged. One isoflurane and 1 sevoflurane patient each experienced elevated postoperative serum creatinine concentrations.

Sevoflurane and isoflurane were equally effective and well tolerated. Induction and emergence success rates were comparable. There were no instances of intraoperative recall.

#### **Safety Assessment:**

Plasma inorganic fluoride concentrations were determined preoperatively, at the end of anesthesia, at 1, 2, 4, 6, and 24 hours post-anesthesia and at the time of discharge or at 72 hours post-anesthesia for patients remaining hospitalized. Peak values were generally observed within 6 hours of the end of anesthesia, but 2 patients had peak concentrations at 24

hours post-anesthesia. One sevoflurane patient experienced maximum plasma inorganic fluoride concentrations  $\geq 50 \mu\text{M}$ . Mean  $C_{\text{max}}$  ( $33.37 \pm 11.3 \mu\text{M}$ ) was similar to values in patients with normal renal function (study 30), but the fluoride half-life ( $t_{1/2}$ ) was prolonged (mean  $t_{1/2} = 28.61$  hours).

The most commonly reported drug-related adverse experience in both groups was hypotension (4/14 sevoflurane and 4/12 isoflurane patients). Two of the 26 patients had serious adverse experiences. One isoflurane patient PS III experienced hyperkalemia on study day 1 post-anesthesia which was considered unrelated to anesthetic administration. One sevoflurane patient PS III suffered cardiopulmonary arrest 11 days postoperatively; his postoperative course had been complicated by fever, acidosis and hypotension, and his arrest was considered unrelated to anesthetic administration. This patient also experienced serum inorganic fluoride concentration of  $51.2 \mu\text{M}$  at 48 hours post-anesthesia.

One isoflurane patient experienced postop SGOT/AST elevations; no patients experienced postop elevations in SGPT/ALT. No patient withdrew from the study due to adverse experiences.

### **Study 32 (supportive)**

This multicenter (6 U.S. sites), randomized open-label study of elderly male and female inpatients (ages 57-93, mean age 72.5 years; only 2 patients were  $< 65$  years of age), ASA PS I-III, compared sevoflurane  $\text{N}_2\text{O}/\text{O}_2$  ( $n=62$ ) to isoflurane  $\text{N}_2\text{O}/\text{O}_2$  ( $n=64$ ) administration during surgery of up to 3 hours duration in concentrations between 0.5 and 1.5 MAC (assumed to be 2.05% for sevoflurane, 1.15% for isoflurane) for maintenance of anesthesia and rapidity, ease of emergence and recovery. One hundred thirty-six patients were enrolled; 124 patients completed the study. Patients underwent intravenous induction and they received various agents for anesthetic maintenance. Fifty two sevoflurane patients and 57 isoflurane patients received  $\text{N}_2\text{O}$ . Most patients (55 sevoflurane, 56 isoflurane) received vecuronium relaxant.

Two patients were prematurely discontinued from the study; 1 sevoflurane patient due to vaporizer malfunction, and 1 isoflurane patient due to adverse experiences of bradycardia and blood loss. A minimum of 50 patients per group was anticipated; this number was not based on statistical analysis power considerations.

A rebreathing circuit was used; maintenance gas flows were not specified.

### **Efficacy Assessment:**

No differences in emergence, recovery times were noted between groups. Post-anesthesia recovery was measured by OPDS, VAS, DSST, and Modified Aldrete Scale (MAS favored sevoflurane patients for circulation and consciousness).

### **Safety Assessment:**

Inorganic fluoride concentrations were statistically significantly higher in sevoflurane patients; however, only 2/62 patients had concentrations  $\geq 50 \mu\text{M}$ , and there was no evidence of renal damage. Sevoflurane patients had prolonged terminal disposition of fluoride, evidenced by longer inorganic fluoride  $t_{1/2}$  than patients with normal hepatic

function. The harmonic mean inorganic fluoride concentration  $t_{1/2}$  was 15.4 hours vs. 11.4 hours in normal adults.

No statistically significant differences in adverse experiences were observed. The most commonly reported adverse experience was hypotension in both groups. Drug-related adverse experiences were mild-to-moderate in 54/62 sevoflurane patients and 59/64 isoflurane patients. There was a greater incidence of nausea and vomiting in the isoflurane patients (53 vs 32 for nausea and 30 vs 13 for vomiting;  $p < 0.05$ ). One sevoflurane patient had impairment of urination which was considered a possible drug-related adverse experience; 1 isoflurane patient each experienced somnolence, nausea and vomiting or hypotension which was considered a possible drug-related adverse experience. No deaths occurred in either group.

### **Study 33 (supportive)**

This multicenter, open label randomized study evaluated 16 PS II-III patients with hepatic impairment (as determined by Child-Pugh class A or B, ie., scores of 5-9) ages 21-79 years, who received sevoflurane  $O_2$ , sevoflurane  $N_2O/O_2$ , isoflurane  $O_2$  or isoflurane  $N_2O/O_2$  to determine the degree of anesthetic metabolism of sevoflurane compared to isoflurane in hepatically impaired patients. Patients received propofol (1-3 mg/kg) or thiopental (2-7 mg/kg) for induction, and they were intubated using either succinylcholine, vecuronium or atracurium. Only 2 of 3 sites enrolled patients; 15/16 patients were at 1 site.

A semi-closed system with soda lime and maintenance gas flows of 2-5 L/minute were used. The planned sample size (40) was not attained.

### **Efficacy Assessment:**

The lidocaine-MEGX assay was measured preoperatively and 24 hours post-anesthesia for the assessment of hepatocellular function. MEGX concentrations were comparable between the 2 groups at baseline, and there were no statistically significant differences between treatment groups as to changes from baseline in MEGX concentrations post-anesthesia. MEGX concentration 24 hours post-anesthesia indicated neither drug adversely affected hepatic function.

### **Safety Assessment:**

Serum inorganic fluoride levels were measured preoperatively, every hour during anesthesia, at the end of anesthesia, at 1, 2, 4, 6, 12, and 24 hours post-anesthesia and (if the patient was hospitalized >24 hours post-anesthesia) at discharge or 72 hours post-anesthesia. No serum inorganic fluoride levels exceeded 45  $\mu M$ . Inorganic fluoride concentrations generally peaked at the end of administration or within 1 hour of end of anesthesia. Sevoflurane patients had prolonged terminal disposition of fluoride, evidenced by longer inorganic fluoride  $t_{1/2}$  than patients with normal hepatic function. The harmonic mean inorganic fluoride concentration  $t_{1/2}$  was 23 hours vs. 11.4 hours in normal adults.

All adverse experiences were either mild or moderate. The most commonly reported drug-related adverse experience was hypotension (5/8 sevoflurane and 4/8 isoflurane patients). No patient deaths or withdrawal due to adverse drug reactions occurred. One

isoflurane patient (no sevoflurane patients) experienced elevated SGOT/AST on day 1 post-anesthesia that was considered possibly related to the study drug. Sevoflurane patients had increased blood pressures from pre-surgery to final evaluation.

## **CONCLUSIONS FROM STUDIES:**

### **Efficacy**

Sevoflurane did not produce any defect in renal concentrating ability in normal volunteers or patients with impaired renal function as determined by pre and post-exposure osmolalities. Renal function was not affected as measured by BUN, creatinine and urine specific gravity.

Despite production of higher inorganic fluoride levels than enflurane, sevoflurane had less impact on urine concentrating ability in patients with normal renal function, as measured by Cmax, Tmax and AUC. These elevated fluoride concentrations were transient (substantially reduced 24 hours post-anesthesia) and not associated with an effect on renal function.

Sevoflurane subjects had faster recovery than enflurane with some measures and better recovery characteristics, especially with shorter exposure.

Sevoflurane was comparable to enflurane or isoflurane for anesthetic maintenance in renal compromised adults. Neither drug caused further impairment of renal function. Renal impairment appears to result in a longer inorganic fluoride half-life without impacting on the maximum blood concentration.

In elderly patients, sevoflurane was comparable to, or had slightly better recovery characteristics than isoflurane. Renal function does not appear to be adversely affected, but inorganic fluoride elimination is prolonged.

MEGX concentration 24 hours post-anesthesia indicated neither sevoflurane nor isoflurane adversely affected hepatic function in patients with preexisting hepatic impairment.

### **Safety**

Inorganic fluoride concentrations were statistically significantly higher in sevoflurane patients; 7/140 patients who received sevoflurane in the 5 studies combined had concentrations  $\geq 50 \mu\text{M}$ , but there was no evidence of impaired renal function. Peak inorganic fluoride concentrations were reached at the end of anesthesia in most patients.

Impaired renal function, impaired hepatic function, and advanced age each prolonged inorganic fluoride half-life.

Drug-related adverse experiences were mild-to-moderate, and they were comparable between sevoflurane and enflurane or isoflurane groups (see Table 2). The most commonly reported drug-related adverse experiences were hypotension (studies 31, 32, 33, 34), nausea, headache and vomiting (study 30). Severe adverse experiences did not appear to be causally related to sevoflurane administration in any of the studies. There was a greater incidence of nausea and vomiting in the isoflurane patients in 1 study. One sevoflurane patient had impairment of urination which was considered a possible drug-related adverse experience.

Table 2.

Study #	30	35	31	34	32	33
# of patients	28	32	41	26	126	16
# serious adverse experiences related to study drug sevoflurane enflurane isoflurane	0/28	0/32 ?	1/20 ?	0/26	0/126	
# patients with ↑ed LFTs sevoflurane enflurane isoflurane	1/14 2/14	1/21 0/11	1/21 0/20	0/14 1/12		0/8 1/8
# patients with inorganic F <sup>-</sup> > 50 μM sevoflurane enflurane isoflurane	3/14 0/14	0/32	1/21 0/20	1/14 0/12	2/62 0/64	0/16

**RECOMMENDATIONS REGARDING LABELING:**

Under "Clinical Trials: Hepatically impaired" section, I recommend describing the patients as having mild-to-moderate hepatic impairment, rather than Child-Pugh scores which are less familiar to the typical reader. I would modify the discussion as follows:

A multicenter (2 sites) study compared the safety of sevoflurane and isoflurane in 16 patients with mild-to-moderate hepatic impairment, utilizing the lidocaine MEGX assay for assessment of hepatocellular function. All patients received intravenous propofol (1-3 mg/kg) or thiopental (2-7 mg/kg) for induction, and succinylcholine, vecuronium or atracurium for intubation. Sevoflurane or isoflurane was administered in either 100% O<sub>2</sub> or up to 70% N<sub>2</sub>O/O<sub>2</sub>. Neither drug adversely affected hepatic function. No serum inorganic fluoride levels exceeded 45 μM, but sevoflurane patients had prolonged terminal disposition of fluoride, as evidenced by longer inorganic fluoride half-life than patients with normal renal function.

Under "Clinical Trials: Renally impaired" section, I would say "sevoflurane was evaluated in renally impaired patients with baseline serum creatinine ≥ 1.5 mg/dL during anesthetic administration of up to 6 hours duration. Based on the incidence and magnitude of changes in serum creatinine concentrations from baseline to post-anesthesia values,

sevoflurane did not further impair renal function". I don't think the table is of any additional value.

Under "Renal or Hepatic Function", the first statement should be modified to read "...sevoflurane is comparable to isoflurane in patients with normal or mild-to-moderately impaired hepatic function. Patients with severe hepatic function were not investigated".

"No evidence... Although renal impairment appears to result in a longer inorganic fluoride half-life, elevated fluoride concentrations were not associated with impairment of renal function.

The table "Change from Baseline to Postanesthesia for Kidney Function Parameters" does not provide information on the level of renal function of these patients from 30 different studies. I find it to be confusing and/or misleading and think it should be drastically modified to include more demographic information or removed.

The table "Incidence of Renal Insufficiency Based on the S.H. Hou Criteria" is cryptic; I attempted to find the Hou Criteria without success, even after questioning the Chief of the Renal Division at my institution. I feel they are sufficiently obscure to question the merit of their use. Further, I'm not sure of the purpose of this table.

NDA#: 20,478  
NAME: Sevoflurane (Sevoflurane)  
SPONSOR: Abbott Hospital Products  
One Abbott Park Road  
Abbott Park, IL 60064-3500  
Phone (708) 937-3216  
REVIEWER: James C. Eisenach, M.D., ALSAC member  
REVIEW DATE: September 15, 1994  
SUBMISSION TYPE: NDA  
CSO: Leslie Vaccari

**RESUME: Obstetric Study (#39) and Muscle Relaxant Study (#40)**

**Background**

Sevoflurane was evaluated in one study in patients undergoing elective cesarean section and in another study in nonpregnant adults receiving muscle relaxants. Isoflurane was used as the comparator in both studies.

**Obstetric Study**

**Study 39:**

Patients scheduled for elective cesarean section under general anesthesia were randomly assigned to isoflurane (n=27) or sevoflurane (m=29) in an open-label study. Anesthesia was induced with intravenous thiopental and MAC-equivalent delivered concentrations of isoflurane (0.5%) or sevoflurane (1.0%) were administered throughout the operation, in conjunction with N<sub>2</sub>O and, after delivery, intravenous opioid. The groups did not differ in neonatal Apgar scores, Neonatal Adaptive Capacity Scores (NACS) at 2 and 24 hrs, or in the incidence of neonates with abnormally low Apgar or NACS scores. The groups did not differ in maternal variables.

**Efficacy assessment:** An independent observer recorded recovery times, including time to extubation, emergence, response to commands, orientation, first post-operative analgesia, eligibility for recovery area discharge, and ability to sit up without nausea/dizziness. The groups did not differ in any of these variables except the time to first analgesia, which was earlier in patients receiving sevoflurane (45 min) than in those receiving isoflurane (59 min), a difference of questionable statistical (p=0.046) or clinical significance. MAC exposure was equivalently low (0.45) and brief (0.45 hr) in both groups.

**Safety assessment:** Safety was evaluated in mothers by measurements of blood pressure and heart rate; adverse experience reporting; screening and post-treatment laboratory evaluations and in neonates by 1 and 5 min Apgar and 2 and 24 hr NACS testing. Serum inorganic fluoride concentration was 3.5 µM/L in mothers at the time of

delivery and was 2.3  $\mu\text{M/L}$  in umbilical blood at the time of delivery. One patient in the sevoflurane group had an increase in SGOT to 371 U/L 4 days after surgery. Four neonates had NACS values  $< 14$  at any time, 2 having been exposed to sevoflurane and 2 having been exposed to isoflurane. Of these, one neonate in each group had jaundice.

### CONCLUSIONS FROM STUDY:

As noted in Dr. Bedford's summary, this study also noted an occasional patient with abnormal LFT's following sevoflurane exposure. A meta-analysis of all the studies would be appropriate. This small exposure study suggests there is no common severe adverse event related to sevoflurane exposure to healthy women at term and their newborns. Within the limitations of this small study, sevoflurane appeared similar to isoflurane for use in general anesthesia for elective cesarean section. It provides no useful information regarding the use of sevoflurane during labor and delivery.

### RECOMMENDATIONS REGARDING LABELING:

Such a limited study does not allow sweeping statements regarding safety of sevoflurane, such as in the **Labor and Delivery** statement. I would suggest a change such as , "Use of sevoflurane in 29 women as part of general anesthesia for elective cesarean section produced no untoward effects in mother or neonate. The safety of sevoflurane in labor and delivery has not been demonstrated."

In the CLINICAL TRIALS section, I would suggest deleting the phrase , "except for time to first post-anesthesia analgesia which was significantly shorter for the sevoflurane group" since this difference was of borderline statistical significance and would be highly dependent on the manner of anesthetic maintenance after delivery of the baby. I would favor removal of the table, as it provides no information of educational or safety value beyond the concluding sentence.

### Muscle Relaxant Study

#### Study 40:

Patients scheduled for operations lasting at least 90 min (primarily ENT procedures) were stratified to receive one of 3 muscle relaxants (vecuronium, pancuronium, or atracurium) and randomized to receive  $\text{N}_2\text{O}-\text{O}_2$ -alfentanil alone ( $n=32$ ), or with .75 MAC sevoflurane ( $n= 32$ ) or isoflurane ( $n=34$ ). Following 30 min of hemodynamic stability, an initial dose, then 3 incremental boluses of each muscle relaxant were given with monitoring of mechanomyography (MMG) and electromyography (EMG). Compared to alfentanil without a volatile anesthetic, both isoflurane and sevoflurane potentiated and prolonged the action of the muscle relaxants to a similar degree. The ED50 and ED95 of each muscle relaxant were reduced by approximately 30% with each volatile agent, and the duration of time to various degrees of recovery

nearly doubled by each volatile agent. Average MAC exposure was 0.80 - 0.90 with duration of 1.5-3.2 MAC-hrs with a similar distribution among groups.

Efficacy assessment:

Recovery characteristics were not evaluated in this study, which focussed solely on muscle relaxant effects.

Safety assessment:

Safety was evaluated by measurements of blood pressure and heart rate; adverse experience reporting; screening and post-treatment laboratory evaluations. Hypotension occurred more commonly in patients receiving sevoflurane (38% incidence) than those receiving isoflurane (3%) or those not receiving a volatile agent (3%). One patient receiving sevoflurane experienced hypoxemia one hr after surgery which required reintubation. This was thought to be due to pre-existing disease and not due to drug. One patient receiving alfentanil without a volatile agent had a low platelet count ( $57 \times 10^9/L$ ) on the first postoperative day.

**CONCLUSIONS FROM STUDY:**

This study suggests that potentiation by sevoflurane of muscle relaxants is similar to that observed with isoflurane. The number of muscle relaxants studied and the multiple methods of data analysis suggest this is a general phenomenon and nearly identical between the two volatile agents.

**RECOMMENDATIONS REGARDING LABELING:**

I like the wording regarding this section of the label, but think there's too much in the 2 tables. I would suggest combining the ED50 and ED95 table with the duration table below it, reducing all numbers to only 2 significant figures (hundredths of a min are not exactly important with pancuronium) and indicating significance with symbols rather than adding 3 columns for p-values.

NDA 20478

ULTANE

2 OF 4

## MEDICAL OFFICER REVIEW

**NDA#:** 20,478  
**NAME:** Sevoflurane (Sevoflurane)  
**SPONSOR:** Abbott Hospital Products  
One Abbott Park Road  
Abbott Park, IL 60064-3500  
Phone (708) - 937-3216  
**REVIEWER:** Robert F. Bedford, M.D., Medical Officer.  
**REVIEW DATE:** August, 1994.  
**SUBMISSION TYPE:** NDA  
**CSO:** Leslie Vaccari

**RESUME:** Neurosurgical Studies : #36, 37, 38.

### **Background**

Sevoflurane was evaluated in three studies of patients undergoing craniotomy. Isoflurane was used as the comparator in each study, 2 of which utilized ICP monitoring.

### **Clinical Studies**

#### **Study 36:**

Patients underwent craniotomy for cerebrovascular indications (8), pituitary disorder (1) or tumor (5). All were monitored for changes in ICP and cerebral blood flow velocity (CBVF) in addition to standard vital signs. Background anesthetic was 60%-70% N<sub>2</sub>O in O<sub>2</sub>, with mild hyperventilation (PaCO<sub>2</sub> = 35±7 and 38±4 in sevo and iso groups, respectively). Addition of 0.5, 1.0 and 1.5 MAC anesthetic resulted in dose-dependent increases in ICP and decreases in MAP with isoflurane (6 patients), whereas no such change in ICP or MAP occurred with sevoflurane (8 patients).

**Efficacy assessment:** No attempt was made to evaluate patients' emergence from anesthesia, presumably because all patients went to the neuro-ICU intubated and paralyzed. Average MAC exposure was not statistically greater in the sevo patients (3.23 MAC-hr) than in the iso patients (2.34 MAC-hr).

**Safety assessment:** Safety was evaluated in all patients by measurements of blood pressure and heart rate; adverse experience reporting; screening and post-treatment laboratory evaluations. Four patients sustained postoperative neurologic complications, none of which were related to the anesthetic. Two iso patients developed transient increases in SGOT/AST, as did 1 sevo patient. One sevo patient had a serum fluoride level of 60 uM on POD #1, another had an elevated BUN which may have been related to 2 postoperative angiograms.

**Study 37:**

Patients undergoing craniotomy were evaluated with regard to speed of emergence from either sevo (10 patients) or iso (10 patients) in N<sub>2</sub>O with O<sub>2</sub>. Anesthetic exposure was 3.24 and 3.32 MAC-hours, respectively. All patients received benzodiazepine preoperatively, all were induced with thiopental. No attempt was made to measure ICP or evaluate the quality of brain relaxation intraoperatively.

**Efficacy assessment:** There was no statistically significant difference between the two anesthetics with regard to time to achieve emergence parameters. Sevo patients awakened with significantly higher pain-discomfort scores than did iso patients at 10 and 20 min in the PACU, but this did not result in any more postoperative hypertension and there was no difference between agents with regard to postoperative opioid requirement or need for vasoactive agents.

**Safety assessment:** Safety was evaluated as in Study 36. One patient in the Iso group sustained a postoperative neurologic complication unrelated to the anesthetic. One sevo patient developed a transient increase in SGOT/AST. One iso patient had an elevated BUN on post op day 4 without an increase in creatinine.

**Study 38**

Eight patients (4 sevo, 4 iso) were evaluated with regard to ICP response to inhalation of 1/2- and 1-MAC concentrations of volatile agent added to N<sub>2</sub>O-O<sub>2</sub>-fentanyl anesthesia. PaCO<sub>2</sub> was progressively lowered from 40 mm Hg to 30 mm Hg in 5 mm Hg increments. ICP was regarded as "controlled" if it remained within 5 mm Hg of values recorded during normocapnia with baseline N<sub>2</sub>O-O<sub>2</sub>-fentanyl anesthesia alone. ICP was essentially the same in both groups prior to introduction of volatile agent. Despite hyperventilation to PaCO<sub>2</sub> of 30 mm Hg, 2 patients at 0.5 MAC iso, and 3 patients at 1 MAC iso had ICP >5mmHg above control values. No sevo patient had ICP > 5mm above baseline with PaCO<sub>2</sub> = 30 mm Hg.

**Efficacy assessment:** There was a stepwise reduction in ICP with progressive hypocapnia in both the sevo and iso groups. Due to the small sample size in each group, there is neither clinical nor statistical support for superiority of sevo over iso. On the other hand, based on these limited data, sevo does not appear to be any more likely than iso to cause elevated ICP in the presence of hypocapnia.

**Safety assessment:** Safety was evaluated as in Study 36. 2 patients (1 in each group) sustained postoperative neurologic complications unrelated to anesthetic. There was no abnormality of liver or renal function after anesthesia.

### **CONCLUSIONS FROM STUDIES:**

As occurs in many other studies in this NDA, the occasional patient given sevoflurane sustains an increase in postoperative LFT's. The incidence and severity of this problem should be evaluated with a meta-analysis of data from all submitted studies in which LFT's were performed.

The Neurosurgical studies demonstrate that sevoflurane has no more impact on ICP than isoflurane in some neurosurgical patients. The decrease in ICP in response to hyperventilation indicates that cerebrovascular reactivity to hypocapnia is maintained at least up to the 1-MAC level. In study 38, both the small number of subjects and the small changes in ICP preclude drawing clinical conclusions about the relative impact of sevo vs iso on patients with intracranial mass lesions.

### **RECOMMENDATIONS REGARDING LABELING:**

Under "Pharmacodynamics: Nervous system effects" the label indicates that there is no difference between sevoflurane and isoflurane regarding ICP response to the agent or to hyperventilation. This statement is repeated in the "Neurosurgery Section." I think this is not so profound that it requires repetition. Recommend deleting the "Pharmacodynamics: Nervous system effects" paragraph, particularly since the lack of sympathetic stimulation is addressed in the "Cardiovascular Effects" section.

The Neurosurgery Section of Clinical Trials contains cryptic text and an overly-detailed table. I would prefer just to see adequately descriptive text such as:

" Three studies compared sevoflurane to isoflurane for maintenance of anesthesia during neurosurgical procedures. In a study of 20 patients, there was no difference between sevoflurane and isoflurane with regard to recovery from anesthesia. In 2 studies, a total of 22 patients with intracranial pressure (ICP) monitors received either sevoflurane or isoflurane. There was no difference between sevoflurane and isoflurane with regard to ICP response to inhalation of 0.5, 1.0 and 1.5 MAC inspired concentrations of volatile agent during N<sub>2</sub>O-O<sub>2</sub> fentanyl anesthesia. During progressive hyperventilation from PaCO<sub>2</sub> =40 to PaCO<sub>2</sub> = 30, ICP response to sevoflurane was preserved at both 0.5 and 1.0 MAC concentrations. In patients at risk for elevations of ICP, sevoflurane should be administered in conjunction with hyperventilation."

## MEDICAL OFFICER REVIEW

IND #: 20,478 Sevoflurane

NAME: Study #18: Maintenance of Anesthesia: Sevoflurane vs Isoflurane  
in Adult Patients (Non-Pivotal)

SPONSOR: Abbott Hospital Products  
One Abbott Park Road  
Abbott Park, IL 60064-3500  
phone (708) - 937-3216

REVIEWER: Robert F. Bedford, M.D., Medical Officer.

REVIEW DATE: Dec 14, 1994.

SUBMISSION TYPE: NDA

CSO: Leslie Vaccari

### 1. RESUME:

#### Background

Sevoflurane is a new inhalational anesthetic which has been undergoing extensive evaluation. This is a non-pivotal multicenter study from Spain examining maintenance and emergence from either sevoflurane/N<sub>2</sub>O or Isoflurane/N<sub>2</sub>O given for general surgical procedures.

#### Clinical Study

Investigator: Gilsanz and Planas: Spain

Eligibility: Healthy adults undergoing surgery lasting at least 1 hour.

Total number of patients receiving Sevoflurane: 40

Total number of patients receiving Isoflurane: 40

#### Primary Clinical Objectives:

- To compare the safety and efficacy of sevoflurane and isoflurane for maintenance of anesthesia .
- To evaluate and ease and rapidity of emergence from sevoflurane and isoflurane.
- To evaluate the relative impact of sevoflurane and isoflurane on standard laboratory tests, including hepatic and renal function.

#### Secondary Objectives:

- To compare the objective pain-discomfort scores of patients recovering from both sevoflurane and isoflurane in the PACU.
- To identify patients that might have had intraoperative recall.

Treatment Plan: This was a multicenter open label randomized trial. General anesthesia was induced in all patients with propofol and maintained with 70% N<sub>2</sub>O in O<sub>2</sub> and fentanyl and vecuronium. Anesthesia

was supplemented with either sevoflurane or isoflurane, as needed, in concentrations not to exceed 3% and 1.5%, respectively.

Times to emergence (opening eyes on command), response to verbal stimuli, first postoperative analgesia and eligibility for PACU discharge (patient awake and vital signs stable for 30 min) were recorded. Ease of emergence was assessed by observing for complications such as coughing, breath holding, excitement, shivering or other adverse events.

**Safety assessment:**

Safety was evaluated in all patients by measurements of blood pressure and heart rate ; adverse experience reporting; recovery room evaluations; screening and post-treatment laboratory evaluations, physical examinations, and vital signs.

**Statistical Analysis:** ANOVA, Fisher's Exact Test and Cochran-Mantel-Haenszel tests, as appropriate.

**SUMMARY OF RESULTS:**

**Efficacy assessment:** Mean duration of anesthesia (92 vs 101 min) and average anesthetic exposure (0.72 vs 0.81 MAC-hr) were not different between the sevoflurane and isoflurane groups, respectively. Mean times to emergence from anesthesia ( 8.3 vs 7.9 min), orientation (12.3 vs 12.1 min), mean pain-discomfort scores and discharge from PACU (129 vs 219 min) also were not different between the sevoflurane and isoflurane groups, respectively.

**Safety assessment:** There was no significant difference between the agents with respect to complications experience during induction, maintenance or emergence from general anesthesia.

In the sevoflurane group, two female patients, 47 and 58 yo, who had normal SGOT/AST and SGPT/ALT values preoperatively, sustained markedly elevated LFT's that peaked on the 2nd POD. In one case elevated LFT's persisted up to 3 days, in the other up to 14 days. No data are supplied on total duration of the elevated LFT's and there is no diagnosis given for causation. One additional patient with mildly abnormal LFT's preop continued to have elevated LFT's postop. All three of these patients underwent biliary surgery.

In the isoflurane group 4 patients with normal preop LFT's had transiently elevated LFT's for 3 days postoperatively. None of these cases was as severe as those in the sevoflurane patients described above. All but one of these patients underwent biliary surgery. In addition, there were 4 patients who have elevated preoperative LFT's and had persistently increased LFT's postoperatively. Again, all but one of these patients underwent biliary surgery.

**CONCLUSIONS:**

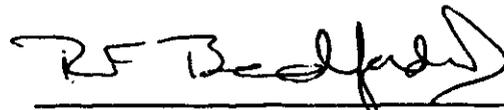
This study demonstrates that sevoflurane and isoflurane are comparable with regard to maintenance and emergence from anesthesia with regard to the variables studied.

The 2 patients who sustained markedly elevated LFT's following sevoflurane are of concern, although they underwent biliary surgery, which may have been responsible. However, other reports of the same problem have emerged in other study reports and it is troubling that there was inadequate followup of these patients to find out how long and how severe the liver function abnormalities persisted.

**RECOMMENDATIONS**

Careful consideration of the impact of sevoflurane on postoperative liver function tests should be given in the safety summary , which is currently in preparation.

Orig IND #20-478  
HFD-007/Div File  
HFD-007/RBedford  
HFD-007/  
HFD-502  
HFD-340  
F/T by



Robert F. Bedford, MD

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## Pilot Drug Evaluation Staff Clinical Safety Review

NDA 20-478

**Sponsor:** Abbott Laboratories  
One Abbott Park Road  
Abbott Park, IL 60064

**Product:** Sevoflurane (fluoromethyl hexafluoroisopropyl ether)  
Maruishi Pharmaceutical Co, Osaka, Japan

**Date:**

NDA filed: 7 July 94  
Preliminary Review: 3 Jan 95  
Final Review: 21 Jan 95

**Medical Officer:** Dan Spyker  
**Peer Medical Officer:** Barbara Palmisano  
**CSO:** Leslie Vaccari

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Cites to the literature contained in the sponsor's Reference Bibliography (Section 13) are given in square brackets [first author, year, cite #] with cite # suffix: C = clinical or P = preclinical. Three cites not contained in Section 13 appear as cite # only [cite #] and are listed at the end of this review.

## Executive Summary

The principal safety issues result from sevoflurane's relative instability *in vitro* (production of a toxic olefin, compound A) and *in vivo* (production of inorganic fluoride). Compound A is readily measurable in closed circuit anesthesia systems at concentrations producing renal toxicity in rats (50 ppm), but no clinical evidence of toxicity has been detected.

Inorganic fluoride (F<sup>-</sup>) results from the hepatic metabolism of sevoflurane (about 3% during a typical anesthesia) via the \_\_\_\_\_ Concentrations of F<sup>-</sup> associated with nephrotoxicity of methoxyflurane (50 μM) are frequently found in patients receiving sevoflurane, but nephrotoxicity has not been detected in the clinical trials or clinical use. The short half-life of F<sup>-</sup> following sevoflurane use is cited as a likely reason for the lack of detectable renal effects. The highly specific (possibly exclusive) dependence on \_\_\_\_\_ and the absence of renal \_\_\_\_\_ may also account for the lesser renal toxicity. In any event, the F<sup>-</sup> concentration provides a surrogate marker (subclinical indicator) of the fluoride nephrotoxicity.

The relative renal safety of sevoflurane in humans appears to reflect:

- lower renal bioactivation of compound A (low renal β lyase activity), and
- lower renal metabolism of sevoflurane to F<sup>-</sup> (low renal \_\_\_\_\_ activity)

Hepatotoxicity of the halothane hepatitis variety has not been reported in the NDA studies and only five cases of hepatitis have been attributed to sevoflurane anesthesia in clinical use. Changes in hepatic enzymes (ALT, AST, GGT) in clinical trials were not different between sevoflurane and comparator agents except in elderly patients. Glutathione s-transferase (GST) appears to be a more sensitive indicator of the hepatic effects of sevoflurane (and other halogenated agents). Thus GST may be a possible surrogate marker of subclinical hepatotoxicity.

**Recommendations:** The reviewers believe that the data so far gathered are adequate to support NDA approval with the following recommendations for post-marketing studies. The sponsor should:

- 1 - develop a subclinical (surrogate) marker for compound A toxicity. Such would necessarily be based on a clear understanding of the mechanism toxicity.
- 2 - conduct an evaluation of the clinical and subclinical hepatotoxicity (including GST responses) involving sensitive patients and maximal sevoflurane exposure.
- 3 - conduct an evaluation of the clinical and subclinical effects of F<sup>-</sup> elevations involving sensitive patients, maximal sevoflurane exposure, active \_\_\_\_\_ and reduced renal clearance. Study endpoints might include:
  - subclinical renal toxicity (maximal renal concentrating ability), and
  - measurement of calcium-dependent hemostasis parameters.

## Overview

The risk: benefit ratio of sevoflurane has been called into question as regards its relative instability *in vitro* (production of a toxic olefin, compound A) and *in vivo* (production of inorganic fluoride). See, for example, the editorial by Mazze [1992, 289-C].

In this review we will consider some of the major safety issues along both dimensions – chemical substances and target organs. Sevoflurane's effects on the central nervous, cardiovascular, and muscular systems do not appear substantially different from those of other inhalational anesthetics. Thus, we are principally concerned here with sevoflurane's hepatic and renal toxicities. Table 1 lists the substances of primary interest. (See Appendix 1 for sevoflurane breakdown summary.)

**Table 1. Summary of Safety Issues**

Substance	Hepatotoxicity	Renal toxicity
Sevoflurane	probable	unlikely
Inorganic Fluoride	likely (site of $\text{F}^-$ production)	Target organ
HFIP	Hepatic deformations after IP injections in rats	unlikely
Compound A	unlikely	probable target
Compounds B, C, D & E	unlikely	unlikely

HFIP = hexafluoroisopropanol

This NDA reports our experience with 5464 patients, 3220 of whom received sevoflurane. Six studies (#30-35) examined patients at particular risk (elderly, hepatic or renal failure) and monitored these patients for clinical toxicity, especially hepatic and renal. Table 2 summarizes the adverse events (AE) rates from these studies.

**Table 2. Tabulation of Adverse Events from High-Risk Patients**

*All patients in Studies 30-35, N=269 patients*

Study #	Number of Patients with Adverse Event									Number Exposed		
	FF Cmax > 50 µM			Renal AE			↑AST/ALT			Sevo	Isoflu	Enflu
	Sevo	Isoflur	Enflur	Sevo	Isoflur	Enflur	Sevo	Isoflur	Enflur	Sevo	Isoflu	Enflu
30	3		0	0		0	0		0	14		14
31	1		0	0		1	3		2	21		20
32	2	0		0			0			62	64	
33	0	0		0	0		0	1		8	8	
34	1	0		2	2		0	0		14	12	
35	0		0	0		0	0		0	21		11
Sum	7	0	0	2	2	1	3	1	2	140	64	45
Exposed	140	84	45	140	84	45	140	84	45			
Percent	5.0%	0.0%	0.0%	1.4%	2.4%	2.2%	2.1%	1.2%	4.4%			

Sevoflurane has been approved in five countries and has been used in two million anesthetics in Japan since approval in 1990. Neither the NDA nor the clinical experience have demonstrated clinical toxicity at rates substantially greater than other inhalational agents. The issues discussed here are thus focused on indicators of subclinical toxicity and susceptible patients.

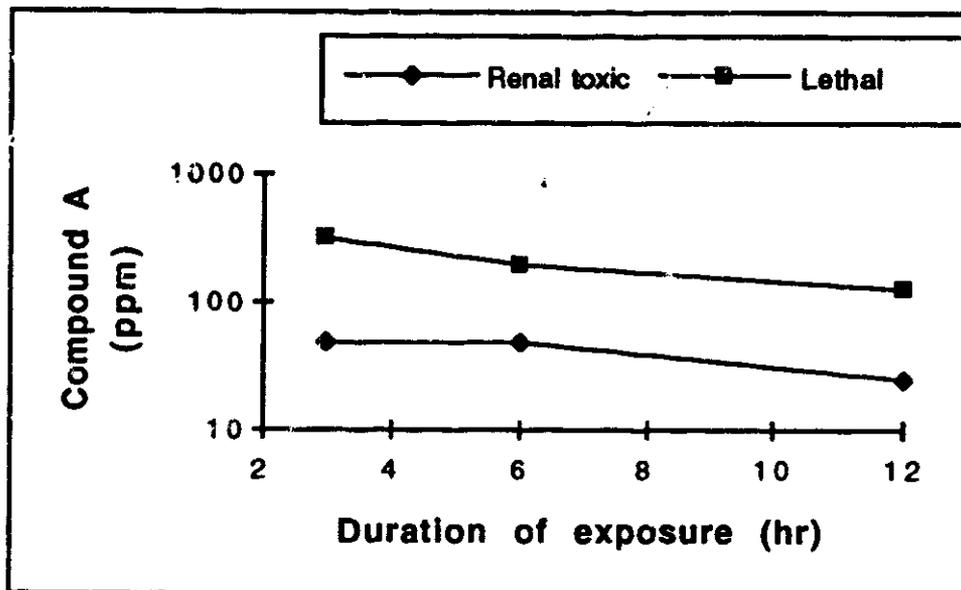
Material reviewed included summaries of the clinical trials (N=40), comments of Ross Terrell in his letter to Commissioner Kessler of 9/28/94, comments of primary consultant reviewers (N=7), primary data sets received from the sponsor, and selected published reports.

## **Compound A**

Sevoflurane is defluorinated under the harsh alkaline conditions in CO<sub>2</sub> absorbents to form 5 breakdown products. The hexafluoride olefin compound A is the most problematic since it appears in the largest concentration and exhibits the highest organ toxicity. Folks at UCSF [Gonsowski, 1994, 38-P, 39-P] carried out duration-response LC<sub>50</sub> studies of compound A in Wistar rats for a 3, 6 & 9 hr exposure as summarized in Figure 1

**Figure 1. Compound A Toxicity in Wistar Rats**

From Gonsowski, et al [38-P & 39-P]



	Duration of Exposure (hours)		
	3 hr	6 hr	12 hr
Renal toxic	50 ppm	50 ppm	25 ppm
Lethal (LC <sub>50</sub> )	331 ppm	203 ppm	127 ppm
SEM (LC <sub>50</sub> )	7 ppm	4 ppm	9 ppm

Bito [1994, 233-C] compared soda lime vs. Baralyme in 16 patients with fresh gas flow of 1 L/min (low flow) in surgical procedures lasting > 10 hr. The ratios of concentration of compound A to sevoflurane were about 0.0011 for soda lime and 0.0015 for Baralyme. Thus for the soda lime group, sevoflurane concentrations of 1.4-1.9% were associated with compound A concentrations of 11-20 ppm. This ratio remained constant or decreased slightly during 15 hr procedures. Earlier studies reported compound A ratios of 2:1 in Baralyme vs. soda lime.

**Table 3. Compound A production in Soda lime and Baralyme**

	Soda lime	Baralyme
Compound A : sevoflurane	0.0011	0.0015
Sevoflurane 1.4-1.9% ->	11-20 ppm	15-27 ppm

The mechanism of compound A toxicity is not well understood, but may be mediated by inorganic fluoride.

No toxicity associated with compound A exposure has been reported in clinical studies or clinical use. One possible contributor to the apparent lesser toxicity of compound A in humans is a difference in bioactivation. Lash [1990, 219-C] studied renal  $\beta$ -lyase activity, a known bio-activator of renal toxins. Human renal  $\beta$ -lyase activity is about 10% of that in the rat and induction of  $\beta$ -lyase activity by keto-acids was only 1.3x in human vs. 30x in rat.

Factors which increase compound A concentration include high sevoflurane concentration, high temperature of the CO<sub>2</sub> absorbent, low gas flow in the anesthesia circuit, and fresh (unused, dry absorbent).

## ***Compounds B, C, D & E***

When sevoflurane reacts with CO<sub>2</sub> absorbents, other breakdown products are produced at high temperatures and high sevoflurane concentration. Compound A reacts with methanol to form compound B, the only other breakdown olefin detected in human anesthesia circuits. Compound B is typically undetected [Bito, 1994, 245-C] or at low concentrations (detected in 7 of 10 patients [Bito, 1994, 233-C]). The highest concentration reported in clinical anesthesia is < 2 ppm. Compound B is much less toxic than compound A – compound caused no adverse effects in rats exposed to 2400 ppm for 3 hr.

## ***Inorganic Fluoride***

**Pharmacokinetics:** Oral fluoride in therapeutic amounts is completely absorbed following therapeutic oral doses.

- Peak blood levels occur ~ 30 min after an oral dose
- Not protein bound, but distributes to bone (10% to 60%), particularly in children. A recent study found 58% of an oral dose in 25 y-olds went to bone [9].
- Biphasic (two-compartment) elimination with half-lives of 2-9 hours reported
- 1.5 mg dose -> peak blood levels of 6  $\mu$ g/dL
- 6  $\mu$ g/dL = 60  $\mu$ g/L = 3.2  $\mu$ M (based on F<sup>-</sup> molecular weight of 19).

Therapeutic fluoride in the prevention of tooth caries has been appreciated since 1931.

Fl <sup>-</sup> in drinking water	Oral alternative	Clinical effect
< 0.7 ppm	0.05-0.07 mg/kg/day	Maximal benefit
> 1.5 ppm	0.1 mg/kg/day	teeth discolor (fluorosis).

Oral NaFl with calcium has been given to treat osteomalacia for 6 months without serious toxicity

- 320 mg/day to adults and
- 80-200 mg/day to children (3-6 y/o)

Acute Fl<sup>-</sup> intoxication with inorganic fluoride (Fl<sup>-</sup>) disrupts numerous physiological systems.

- tightly binds (most electronegative element) many cations (hypocalcaemia -> inhibition of normal blood coagulation)
- stimulates enzymes (adenylate cyclase)
- inhibits enzymes (Na<sup>+</sup>-K<sup>+</sup>-ATPase, carbohydrate metabolism)
- fatal overdose (>30 mg/kg) can result from these processes or from a delayed, explosive hyperkalemia.

Table 4 indicates the clinical effects associated with oral exposure (in terms of mg of Fl<sup>-</sup>). The second column (Expected C<sub>max</sub>) is based on a linear extrapolation of the above (1.5 mg dose -> 3.2 μM C<sub>max</sub>).

**Table 4. Fl<sup>-</sup> Dose, Expected C<sub>max</sub>, and Clinical Effects**

Dose Fl <sup>-</sup> (mg/kg)	C <sub>max</sub> (μM)	Reported Clinical Effects
1	150	Symptoms (17% of patients)
3	450	GI toxicity likely
8	1200	Triage: Ipecac + milk + MD
10	1500	Major toxicity likely
17	2500	Minimum lethal dose (MLD)
32-64	5-10,000	Median lethal dose (LD <sub>50</sub> )

Sevoflurane is metabolized (about 3% of a typical anesthesia dose) to Fl<sup>-</sup> and hexafluoroisopropanol (HFIP). The kidney, the organ of elimination, is particularly susceptible to Fl<sup>-</sup> toxicity. Serum Fl<sup>-</sup> concentrations were measured in Studies 03, 08, 09, 10, 13, 15, 22-24, 27, 28, 36, 38, and 39 all 6 high-risk patient studies (Studies 30-35). As seen in Table 2 and numerous published studies, sevoflurane use is associated with a greater frequency of Fl<sup>-</sup> peaks > 50 μM than other anesthetics. None of these studies have reported an association or correlation between Fl<sup>-</sup> peaks or area under-the-curve (AUC) and clinical toxicity. In Frink's comparison

[1994, 122-C] of sevoflurane and enflurane, 3 of 7 enflurane patients showed reduced urine concentrating ability at Day 1 (66%, 77%, 80% & 81% of baseline values) compared to 0 of 7 sevoflurane patients (none <87%) despite mean FI<sup>-</sup> peaks of 47 μM for the sevoflurane group and 23 μM for the enflurane group.

## HFIP

Organic fluoride metabolites of methoxyflurane and enflurane can bind to liver macromolecules and trigger an idiosyncratic reaction (like halothane hepatitis). HFIP (hexafluoroisopropanol), the other major sevoflurane metabolite (along with FI<sup>-</sup>) is about 80x more toxic by intraperitoneal (IP) injection (IP LD<sub>50</sub> = 0.14-0.2 mg/kg) than sevoflurane (IP LD<sub>50</sub> = 10-18 mg/kg). IP injections of HFIP are associated with tissue adhesion and hepatic deformation. Jiaxiang [1993, 57-P] reported an HFIP half-life of 55 hr in clinical studies while the half-life of HFIP in rats is < 10 minutes. HFIP is rapidly conjugated with glucuronic acid and eliminated. This difference (55 hr vs. 10 min) probably reflects continued production of HFIP in humans after sevoflurane is discontinued and suggests the enzyme production system is saturated at low levels of sevoflurane. Rapid glucuronidation of HFIP probably accounts for the low concentrations and minimal systemic toxicity.

## P450 2E1

More than 14 human cytochrome P450 isoforms have been identified. P450 2E1, believed to reside on Chromosome 10, contributes to the metabolism of methoxyflurane, sevoflurane, enflurane, isoflurane, and desflurane. This isoform is predominately (? exclusively) hepatic, and significant amounts of human renal 2E1 have not been found [de Waziers, 1990, 20-C]. Kharasch [1993, 22-C] identified 2E1 as the principal, if not sole, metabolizer of sevoflurane and the principal metabolizer of methoxyflurane. At saturating substrate concentrations, the rank ordering of metabolic rates ( $V_{max}$ ) was: methoxyflurane > sevoflurane > enflurane > isoflurane > desflurane > 0. Factors known to increase 2E1 activity and known (or presumed) to increase *in vivo* sevoflurane break down include: obesity (x 2-3), chronic isoniazid therapy, and chronic ethanol exposure. In addition, men may have higher activity of 2E1 than women [23]. Genetic polymorphism in the P450 2E1 gene has been described in Japanese [3].

**Substrates for P450 2E1**

Acetaminophen  
Acetone  
Aniline  
Benzene  
Chlorinated hydrocarbons  
Chlorzoxazone (Parafon Forte)  
Enflurane  
Ethanol  
Fluorinated hydrocarbons  
Halothane  
Isoflurane  
Methoxyflurane  
N-alkyl-formamides  
Sevoflurane

**Inhibitors of P450 2E1**

Diallyl sulfone (garlic)  
Disulfiram (Antabuse)  
4-methylpyrazole

**Inducers of P450 2E1**

Ethanol  
Isoniazid

Clinical circumstances likely to increase the metabolism of sevoflurane based on our understanding of the role of P450 2E1 include obesity and compounds which induce 2E1 (isoniazid and ethanol). Substances associated with general P450 induction including barbiturates and phenytoin, do not induce 2E1 in humans although they may induce metabolism of sevoflurane, enflurane, and isoflurane in rodents [Wrighton, 1992, 157-P].

## ***Renal toxicity***

Despite the  $Fl^-$  concentrations and presence of compound A, there has been a distinct paucity of reported renal toxicity associated with the clinical use of sevoflurane. We believe that a case of syndrome of inappropriate antidiuretic hormone (SIADH) in a 6 y-o male after two sevoflurane anesthetics reported by Yoshida [1993, 333-C] is unlikely to represent renal toxicity.

Fluoride nephrotoxicity following oral fluoride overdoses are distinctly uncommon. A literature review via Medline from 1966 to 1/15/94 showed 587 articles dealing with fluoride poisoning/overdose, 40,337 reporting nephrotoxicity, and 10 in common to the two categories [10-19]. Two non-English papers [20, 21] were reported in the Poisindex [22]. Most of these reports appear to deal with coexisting renal failure [11-15], and three deal with methoxyflurane as the  $Fl^-$  source [17-19].

Methoxyflurane nephrotoxicity (high-output renal insufficiency unresponsive to vasopressin) has been recognized since 1966. The predominant pathological lesion in rats was found in the proximal convoluted tubule [Mazze, 1972, 236-P]. We are left with a distinct need to explain the lack of renal toxicity of sevoflurane.

**Renal effects of sevoflurane** have not correlated with peak  $FI^-$  concentrations or AUC in clinical trials. Frink, *et al.*, [1994, 122-C] studied  $FI^-$  concentrations, renal concentrating ability, creatinine clearance ( $C_{Cr}$ ), and n-acetyl- $\beta$ -glycosaminidase (NAG) for 5 days after 9.5 MAC-hr sevoflurane or enflurane exposure in 14 volunteers carefully screened to exclude exposure to 2E1 enzyme-inducing agents. Peak  $FI^-$  concentrations were 47 and 23  $\mu M$  after sevoflurane and enflurane respectively. Mean renal concentrating ability compared to baseline was 94% for sevoflurane and 85% for enflurane patients (not statistically significant,  $p=0.12$ ). Neither  $C_{Cr}$  or NAG showed any change from baseline. This inverse relation (renal effects in patients with a lower  $FI^-$  exposure) suggests some direct effect (or protection) of the sevoflurane. Studies carried out by Kharasch at the U of Washington [1994, 180-C] offer a plausible explanation – human renal tissue shows a much lower metabolic activity for the production of  $FI^-$  as compared to methoxyflurane.

Thus the relative renal safety of sevoflurane in humans appears to reflect:

- lower renal bioactivation of compound A (low renal  $\beta$  lyase activity), and
- lower renal metabolism of sevoflurane to  $FI^-$  (low renal activity)

## **Hepatotoxicity**

Preclinical studies showed ALT, AST, LDH & Alk phos elevated after prolonged exposures (pharmacology review, pack page 219). Sevoflurane did not appear to alter hepatic blood flow in preclinical studies.

Five cases of hepatic toxicity [1, 2,4-6] have been attributed to sevoflurane in clinical use in Japan (see appendix 2).

From the analyses of the AEs and laboratory data in the NDA studies, the only statistically significant result was the comparison of AST/SGOT increases across all elderly patients (Integrated Summary of Safety, page 55). Table 3 shows the rates and the statistical analyses. The statistical significance ( $p < 0.05$ ) was only apparent using the Cochran-Mantel-Haenszel test (correcting for study).

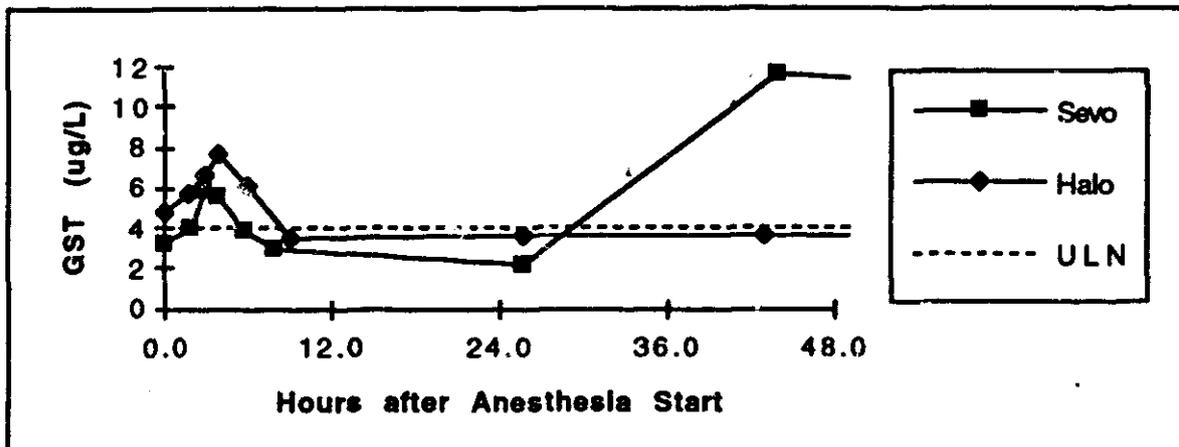
**Table 3. Frequency of AST / SGOT Elevation in Elderly Patients**  
*All comparative studies in the elderly, N=680*

Treatment	Sevoflurane	Comparator
Normal AST/SGOT	359	301
Elevated AST/SGOT	15	5
Total	374	306
% Elevated	4%	2%
<b>Cochran-Mantel-Haenszel's stratifying by study</b>		
Chi-Square p-value = 0.0480		
<b>Exact Binomial Comparison</b>		
Two tailed p-value = 0.1055		
<b>Binomial Comparison by Corrected Chi-Square</b>		
Chi-Square p-value = 0.1103		

In the absence of a rise in the more frequently measured hepatic enzymes, it would be desirable to have some other indicator of subclinical sevoflurane hepatic injury. Hussey [1988, 49-C] studied plasma glutathione s-transferase (GST) as a more sensitive indicator of hepatocellular toxicity after halothane, enflurane and isoflurane anesthesia. He reported GST rises to above normal levels in 19 of 70 adult patients including late (24 hr) rises in 4 receiving halothane (1.8 hr of 1-1.2 MAC) and 3 receiving enflurane. Only one of Hussey's patients had an associated increase in ALT, all other hepatic enzymes remained in the normal range. Allen [53-C] studied GST in 60 yr olds and found elevations in 13 of 37 (35%) receiving halothane/N<sub>2</sub>O, 4 of 17 (24%) receiving halothane in O<sub>2</sub>, and none of 17 receiving isoflurane.

GST response was assessed in one of the NDA studies. Taivainen [1994, 127-C] (NDA Study 22 in pediatric patients 5-13 yrs old) found GST elevations with both sevoflurane and halothane including two patients in each group with late GST rises. Figure 2 shows the mean GST concentrations from these two-groups of patients.

**Figure 2. GST Concentrations after Sevoflurane and Halothane**  
All patients from Study 22, N=50



Nominal Time	Sevoflurane					Halothane				
	N	Min	Max	Mean	SD	N	Min	Max	Mean	SD
Prestudy	25	0.8	18.2	3.2	3.5	25	1.4	17.1	4.8	3.6
End anesth	25	0.5	16.9	4.1	4.1	25	1.4	20.8	5.8	4.7
1 hr	25	1.4	28.0	5.8	6.0	25	1.0	23.8	6.6	5.6
2 hr	25	1.5	30.8	5.6	3.6	25	0.6	32.6	7.7	7.6
4 hr	25	0.5	21.8	3.9	4.3	25	1.4	36.5	6.1	7.3
6 hr	25	0.1	10.3	2.9	2.3	25	0.7	9.0	3.5	2.2
24 hr	25	0.6	11.9	2.3	2.5	24	0.7	16.6	3.7	3.4
48 hr	24	0.1	224	11.6	45.4	21	0.6	14.7	3.7	3.6
Late F/U	2	1.0	3.1	2.1	1.5	2	1.1	4.3	2.7	2.3
<b>Patient GST Response</b>										
Min	25	0.1	7.2	1.7	1.5	25	0.6	6.3	2.2	1.5
Max	25	1.6	224	16.2	43.9	25	2.0	36.5	10.5	9.2
Max-Pre	25	0.2	223	13.0	43.9	25	0.0	30.2	5.6	7.8
48-24 hr	24	-3.7	223	9.7	45.6	21	-1.4	7.2	0.4	2.1
Dur anesth	25	0.8	3.7	1.8	0.8	25	0.0	4.1	1.8	0.9

ULN = Upper limit of GST normal range

The late rise in GST for the sevoflurane patients (48 hr value of 11.6) results in a single high level in Patient 16 (see Figure 3).

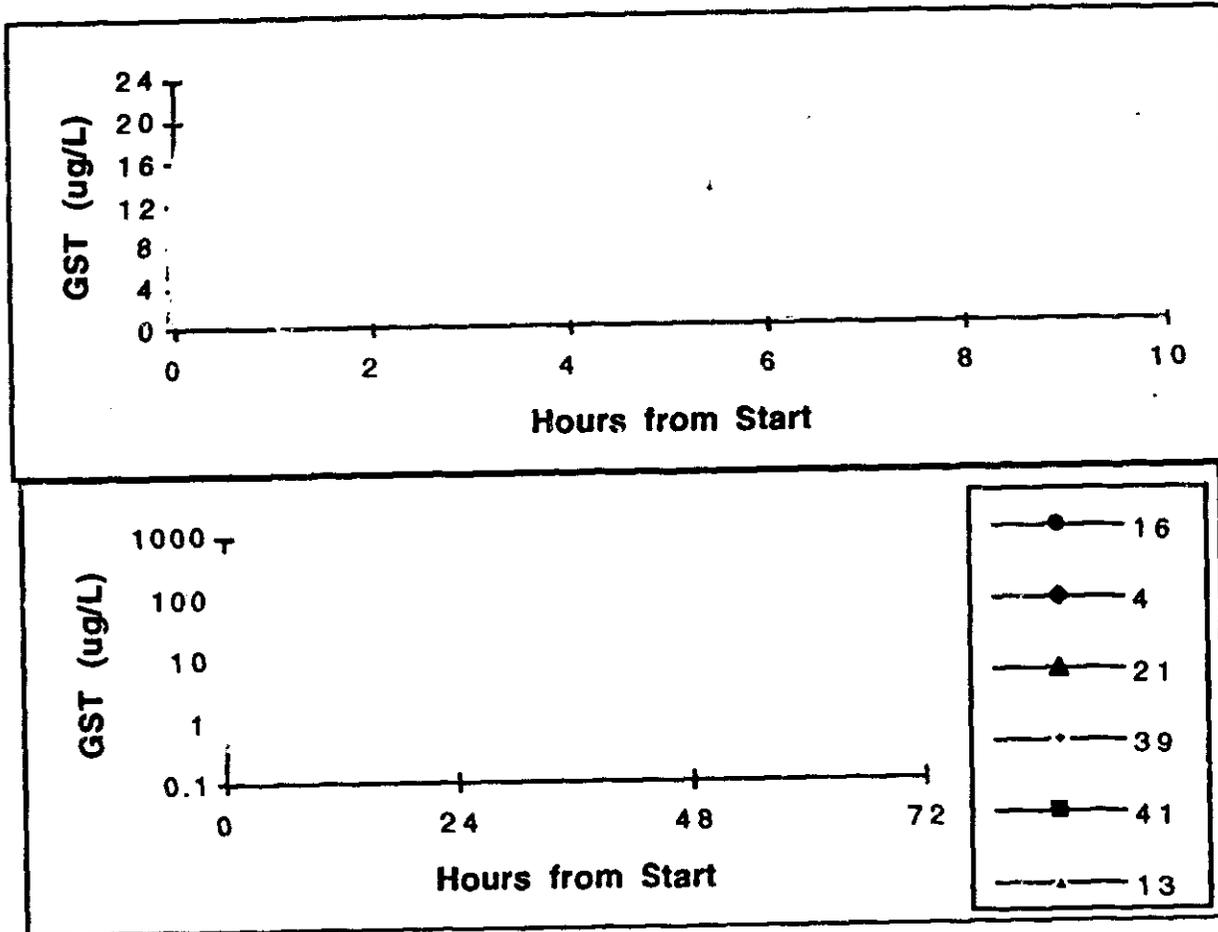
A normal GST level has not been established in pediatric patients, but is < 4 µg/L in adults. Study 22 cites upper limits of reference values for adults as 6 µg/L for females and 14 µg/L for males. (In Study 22 there were no baseline differences between sexes, 3.1 ± 1.9 vs. 3.8 ± 2.6 µg/L for females and males, respectively). The "Prestudy" GST in the sevoflurane group was 0.8

- 18.2 (mean 3.2)  $\mu\text{g/L}$  and suggests we need to focus on changes from baseline rather than the upper-limit-of-normal threshold.

The row "Max - Pre" gives the difference between maximum value and the "Prestudy" GST. Likewise "48 - 24 hr" examines the difference between the 2 day value and the 1 day value (late increase). The sevoflurane and halothane groups were statistically significantly different ( $p < 0.05$  by t-test) for the "End anesthesia" values, but the difference was largely accounted for by the "Prestudy" differences (using "Prestudy" values as a covariate). In the final analysis there were no statistically significant differences for the two groups in GST pattern.

We were particularly interested in the late rises in GST. Figures 3 and 4 display the individual patient data for each patient whose GST rose more than  $0.4 \mu\text{g/L}$  between the 24 and 48 hr levels. Each figure shows the first 10 hr in the top panel and a 72 hr plot in the lower panel. Note, the lower panel uses a log ordinate scale. Note also that the abscissa origin ( $t=0$ ) is based on the beginning of anesthesia so that the first ( $t>0$ ) data point is the post-anesthesia value.

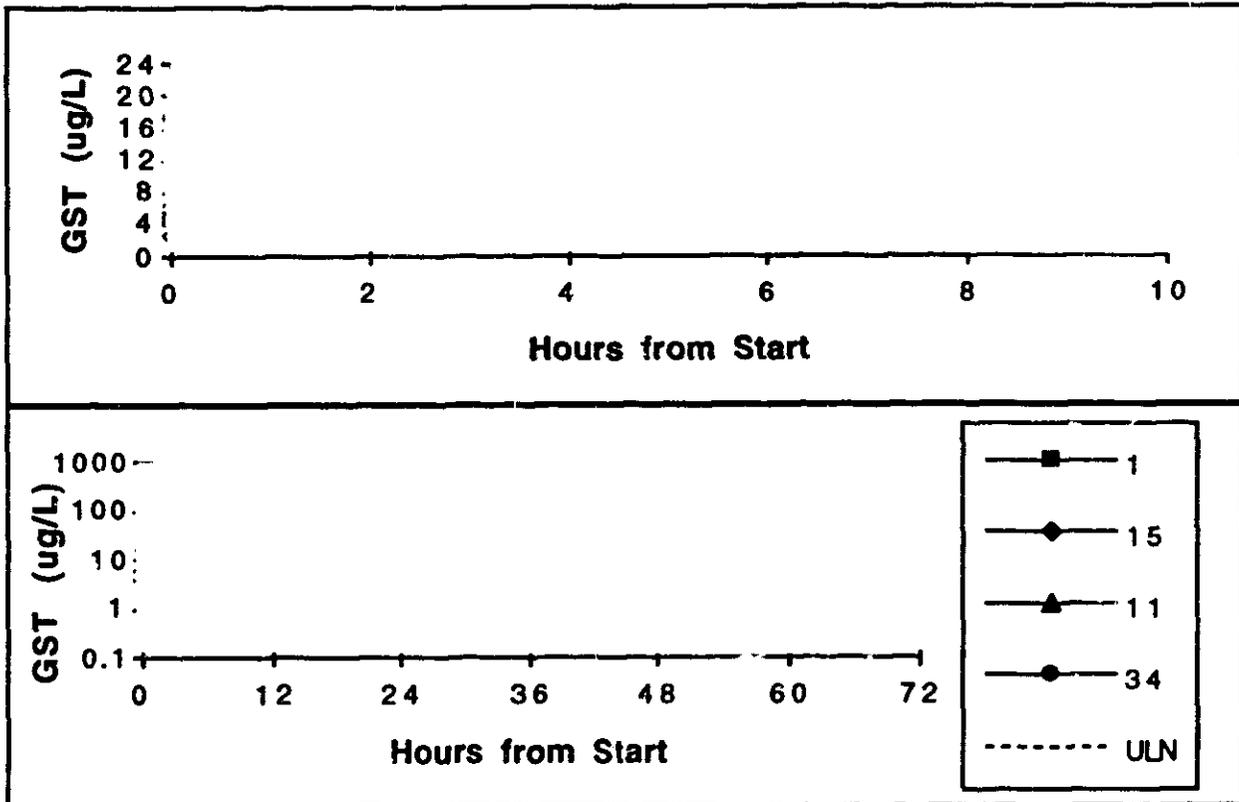
**Figure 3. GST Concentrations after Sevoflurane Anesthesia**  
Patients from Study 22 with 48 hr GST increase, > 0.4 ug/L, N=7



Pat #		Pre-study	End anesth	1 hr	2 hr	4 hr	6 hr	24 hr	48 hr	Late F/U	48-24
	Time										
16	GST										
	Time										
4	GST										
	Time										
21	GST										
	Time										
39	GST										
	Time										
41	GST										
	Time										
13	GST										
	Time										
29	GST										
	Time										
27	GST										

Patient 16 with the highest GST value had spondylolisthesis and an unremarkable anesthesia for spinal fusion (lumbar IV through sacrum I). In the article cited, this patient was "excluded" from analysis by Taivainen based on receipt of trimethoprim-sulfa on the day of surgery for asymptomatic lower urinary tract infection.

**Figure 4. GST Concentrations after Halothane Anesthesia**  
Patients from Study 22 with 48 hr GST increase, > 0.4 ug/L, N=4



	Pat #	Pre study	End anesth	1 hr	2 hr	4 hr	6 hr	24 hr	48 hr	Late F/U	48-24 hr
Time											
GST											
Time											
GST											
Time											
GST											
Time											
GST											

While underwhelming in this graphic representation, several of these patients doubled their GST between 24 and 48 hr.

## **Reviewers' Discussion**

Halothane, the most commonly used volatile induction agent in pediatric practice, is almost devoid of toxicity in pediatric patients. Sevoflurane could replace halothane in pediatric practice due to its more rapid equilibration (faster onset and recovery). Isoflurane, probably the most common volatile anesthetic agent used in adult anesthesia, is nearly devoid of delayed organ toxicity. Sevoflurane could likewise compete with isoflurane in adult anesthesia.

The principal sevoflurane safety issues result from the relative instability *in vitro* (compound A) and *in vivo* (inorganic  $\text{F}^-$ ). Although compound A is readily measurable in closed circuit anesthesia systems at concentrations producing renal toxicity in rats (50 ppm), sevoflurane remains almost devoid of renal toxicity in clinical studies or use.

**Inorganic fluoride ( $\text{F}^-$ )** results from the hepatic metabolism of sevoflurane (about 3% during a typical anesthetic administration) via the P450 2E1 isoform. Concentrations of  $\text{F}^-$  associated with nephrotoxicity of methoxyflurane (50  $\mu\text{M}$ ) are frequently found in patients receiving sevoflurane, but nephrotoxicity has not been detected in clinical trials or clinical use.  $\text{F}^-$  concentration provides a surrogate marker (subclinical indicator) of fluoride nephrotoxicity.

Hepatotoxicity of the halothane hepatitis variety has not been reported in the NDA studies and only two cases of hepatitis have been attributed to sevoflurane anesthesia in clinical use. We must recall that several million exposures to halothane were required to detect this delayed hepatotoxicity. The large experience of sevoflurane use in Japan (> 2 million patients) is less of a comfort since a semiclosed (rather than a closed) circuit system is used in Japan. Plasma glutathione s-transferase (GST) is a sensitive indicator of hepatocellular damage and is possibly a surrogate marker of sevoflurane subclinical hepatotoxicity.

**Recommendations:** The reviewers believe that the data so far gathered are adequate to support NDA approval with the following recommendations for post-marketing studies. The sponsor should:

- 1 - develop a subclinical (surrogate) marker for compound A toxicity. Such would necessarily be based on a clear understanding of the mechanism toxicity.
- 2 - conduct an evaluation of the clinical and subclinical hepatotoxicity (including GST responses) involving sensitive patients and maximal sevoflurane exposure.
- 3 - conduct an evaluation of the clinical and subclinical effects of  $\text{F}^-$  elevations involving sensitive patients, maximal sevoflurane exposure, active P450 2E1, and reduced renal clearance. Study endpoints might include:
  - subclinical renal toxicity (maximal renal concentrating ability), and
  - measurement of calcium-dependent hemostasis parameters.

## References

The sponsor is to be commended for the excellent annotated bibliography (Section 13 in the Clinical Summaries Pack) prepared of the numerous published articles dealing with sevoflurane. The following cites are not included in Section 13:

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9. Ekstrand J, Ehrnebo M, Boreus LO: Fluoride bioavailability after intravenous and oral administration: importance of renal clearance and urine flow. *Clin Pharmacol Ther* 23; 329-39: 1978.
10. Lantz O; Jouvin MH; De Vernejoul MC; Druet P: Fluoride-induced chronic renal failure. *Am J Kidney Dis* 1987 Aug;10(2):136-9  
Abs: Renal fluoride toxicity in human beings is difficult to assess in the literature. Although experimental studies and research on methoxyflurane toxicity have shown frank renal damage, observations of renal insufficiency related to chronic fluoride exposure are scarce. We report a case of fluoride intoxication related to potomania of Vichy water, a highly mineralized water containing 8.5 mg/L of fluoride. Features of fluoride osteosclerosis were prominent and end-stage renal failure was absence of other cause of renal insufficiency suggest a causal relationship between fluoride intoxication and renal failure.
11. Noel C; Gosselin B; Dracon M; Pagniez D; Lemaguer D; Lemaitre L; Dhondt JL; Lelievre G; Tacquet A: [Risk of bone disease as a result of fluoride intake in chronic renal insufficiency] *Nephrologie* 1985;6(4):181-5  
Abs: Four cases of osteosclerosis were observed in patients with renal failure. All subjects presented with moderate reduction in renal function which had been stabilized for several years. Osteosclerosis appeared

progressively but was clinically symptomatic in only one patient. Fluoride intoxication was ascertained on the basis of X-ray examination and bone biopsy. In addition, the source of fluoride intoxication was easily recognized as the drinking water (2 to 3 l/day), Vichy Saint Yorre commercial mineral water (fluoride concentration 9 mg/l) in 3 cases, and tap water in the fourth case. These observations emphasize the risk of high chronic fluoride intake in patients with renal failure, even with mild reduction of glomerular filtration rate.

12. McIvor M; Baltazar RF; Beltran J; Mower MM; Wenk R; Lustgarten J; Salomon J: Hyperkalemia and cardiac arrest from fluoride exposure during hemodialysis. *Am J Cardiol* 1983 Mar 1;51(5):901-2
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15. Schmidt CW; Kunze P; Funke U; Auermann K: [Bone fluorosis without occupational exposure in chronic renal insufficiency] *Z. Gesamte Inn Med* 1978 Nov 15;33(22):837-40  
Abs: Report on a 70-year-old male with bone fluorosis which was ascertained radiologically, by section and fluor analysis in the bone ash. With empty professional anamnesis as cause was found the presence of a chronic renal insufficiency with simultaneously increased fluor content of drinking water. The decreased renal excretion of fluoride might have led to the pathological development in the bones. It is referred to the significance of extra-medical fluor load and the knowledge of the renal function when halogen is therapeutically used.
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21. Manigand G, Fillastre JP, Milhaud G, et al.: Fluorose osseuse associee a une nephropathie interstitielle chronique avec nephrocalcinose. *Ann Med Interne* 1970; 122: 191-8.
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23. O'Shea D, Davis, SN, Kim RB, Wilkinson GR: Effect of fasting and obesity in humans on the 6-hydroxylation of chloroxazone: A putative probe of CYP2E1 activity.

Re            ated.

DA Spyker  
D. A. Spyker, MD.  
Medical Reviewer

2/11/95  
Date

Barbara Palmisano MD  
Barbara Palmisano, MD.  
Peer Medical Reviewer

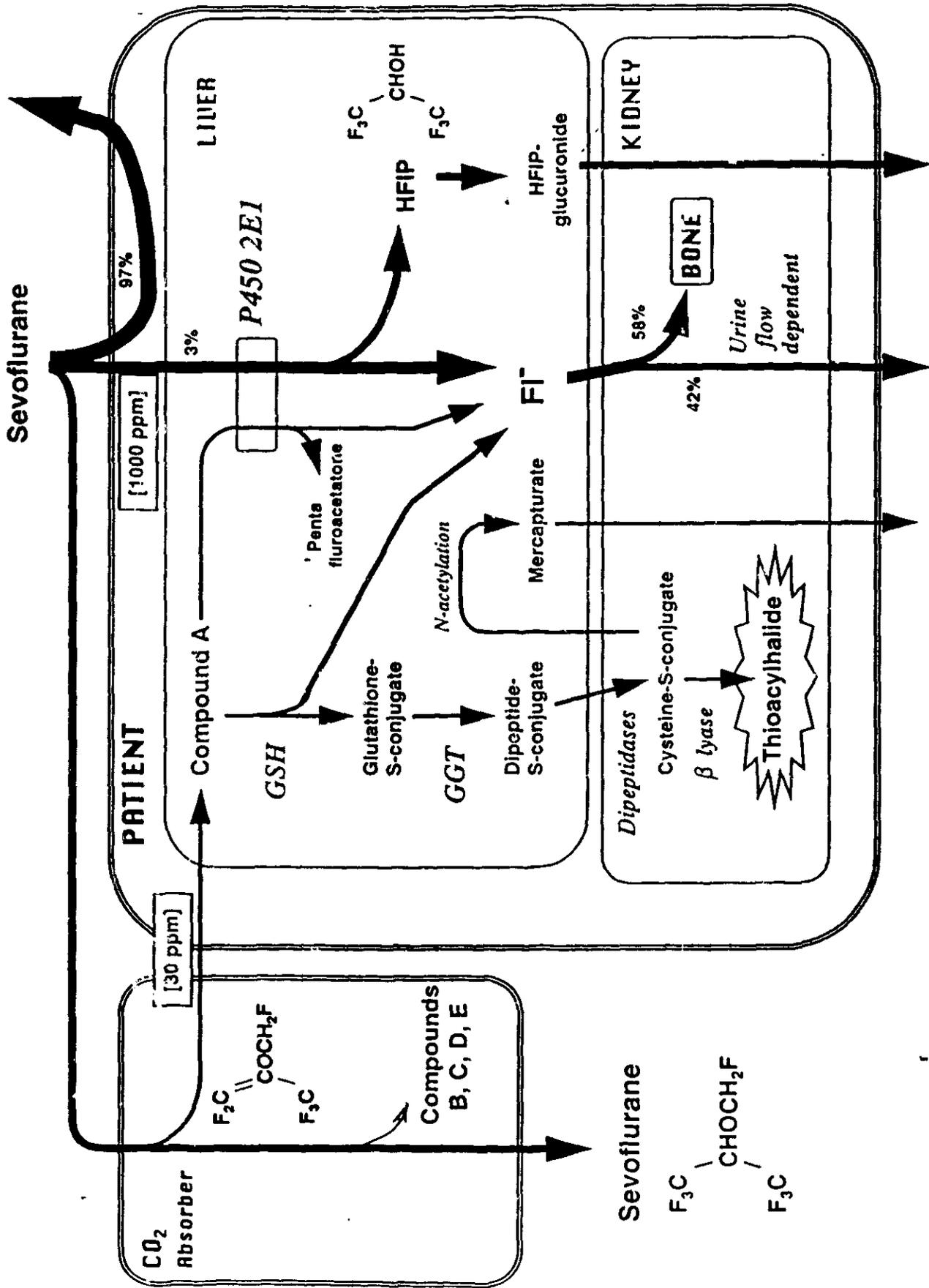
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- cc: Original NDA 20-478  
HFD-007/Division File  
HFD-007/Spyker  
HFD-007/Palmisano  
HFD-007/Vaccari  
HFD-007/Bedford

MacDan\main\abbott\tox review

Friday, January 20, 1995

# Sevoflurane Safety Summary *in vitro* & *in vivo* Pathways



Clinic Hepatotoxicity - Literature Review

ref # age sex	procedure	past history	exposure	illness	meds	lab	outcome & assessment
#1 63 years male	craniotomy - SAH; aneurysm		OR #1 enflurane POD#1 enflurane POL#36 spinal POD#46 enflurane POD#83 sevo (wound infection)			POD 2-3 ↑ LFT  DLST (+) hal, sevo, iso (±) enfl, antibiotic	resolved  ?? cross sensitivity
#2 30 days male	strangulated inguinal hernia - emergent	small for gestational age	1.3-1.5% - 140 min	POD 2 - vomiting, irritability; POD 7 - fever 39°, anorexia; POD 14 - ulcerative stomatitis	antibiotics	POD 2 - ↑ LFT & WBC  bili, coags - wnl viral (-) DLST (-)	resolved
#4 11 months male	excise supernumary digits	sl ↑ CPK	3% induct 0.4-0.6% maint (epidural mepiv)	POD 7 - fever POD 9 - rash	diclofenac antibiotics glutathione	POD 9 sl ↑GOT POD 14 ↑LFT DLST ± sevo	resolved
#5 38 years male	transphenoidal hypophysectomy  pituitary adenoma	sl ↑GPT; obesity	0.8-1% x 7 hr	diabetes insipidus POD 4 - fever, cholangitis; fatty liver per ultrasound	diclofenac cimetidine decadron antibiotic piperidine	POD 4 - ↑ LFT, coags, NH <sub>3</sub> ; ↑WBC DLST (-) viral (-)	hepatic coma; death  no histology
#6 48 years male	dermal flap submaxillary tumor	ETOH hep; fatty liver; transient ↑LFT 2° chemo	OR #1 - Iso 10 hrs POD 22 - Iso POD 100 - Sevo 0.8-1.8% x 4.25 hr		antibiotics	POD 1 - ↑ LFT  DLST (+) iso & antibiotics (±) hal, sevo.	resolved  ?? cross sensitivity

(DLST = delayed lymphocyte stimulating test)

December 20, 1994

**MEDICAL OFFICER SAFETY REVIEW  
PILOT DRUG EVALUATION STAFF****MAR 22 1995****DEC 28 1994****NDA #:** 20-478**Drug:** Sevoflurane (Sevorane): Review of Safety Update to Pending  
NDA submitted July 11, 1994**Sponsor:** Abbott Laboratories  
Abbott Park, IL 60064**Sponsor's Letter Dated:** Nov 21, 1994**Reviewer:** Robert F. Bedford, M.D., Medical Officer.**Review Date:** Dec 7, 1994**Submission Type:** Safety Update**CSO:** Leslie Vaccari**Resume and Background**

This NDA is for a new inhalational general anesthetic. It has been in use of Japan for several years, with over a million patient exposures. It is rapid in onset, not unpleasant to inhale, and has a rapid termination of action. This submission updates safety data reported since the NDA was filed in July.

**Clinical Studies**

10 clinical studies are included, representing 598 patients and 10 subjects receiving sevoflurane and 210 patients receiving comparator agents. 3 of the studies include pediatric patients.

**Serious Adverse Events:**

10 serious adverse events are reported from the above studies. None appear to be related to anesthetic management.

Occasional transient postoperative laboratory abnormalities, specifically elevated creatinine and liver function tests continue to be reported, although the incidence of these findings is identical for both sevoflurane and comparator agents, usually isoflurane.

**Post Marketing Adverse Events:**

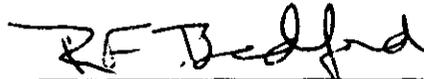
8 cases of malignant hyperpyrexia have been reported in the Japanese literature. This issue is addressed in the present draft package insert. 1 case of transient postoperative hepatic dysfunction is also reported, and this may well be related to an effect of sevoflurane, since it did not occur after 2 previous isoflurane anesthetics, but did occur in the same patient after a third anesthetic with sevoflurane.

**Additional Pharmacologic Studies:**

An article in the Journal of Neurosurgical Anesthesia was also submitted. The study examines intracranial pressure responses in rabbits with cortical freeze lesions. The results suggest that 1.5 MAC sevoflurane causes more elevations in ICP when blood pressure is elevated than occurs

that the effect of 1 MAC sevoflurane is approximately the same as that of isoflurane. At this time, no change in the labeling is required.

Orig NDA # 20-478  
HFD-007/Div File  
HFD-007/R.Bedford  
HFD-007/  
HFD-502  
HFD-340  
F/T by



Robert F. Bedford, MD

  
Peer Reviewer

January 12, 1995

**MEDICAL OFFICER LITERATURE REVIEW  
PILOT DRUG EVALUATION STAFF****NDA #:** 20-478**Drug:** Sevoflurane (Sevorane): Review of Literature Update to Pending  
NDA submitted July 11, 1994**Sponsor:** Abbott Laboratories  
Abbott Park, IL 60064**Sponsor's Letter Dated:** December 22, 1994**Reviewer:** Robert F. Bedford, M.D., Medical Officer.**Review Date:** January 12, 1995**Submission Type:** 1994 Literature**CSO:** Leslie Vaccari**Resume and Background**

This NDA is for a new inhalational general anesthetic. It has been in use of Japan since 1990, with several million patient exposures. It is rapid in onset, not unpleasant to inhale, and is characterized by rapid onset and termination of action. This submission updates the medical literature reported since the NDA was filed in July.

**Clinical Studies**

Ninty eight publications and one copy of correspondence are submitted. The topics covered in these documents include the following: MAC measurements in special populations, EEG effects of sevoflurane, quantification of sevoflurane chemical characteristics, sevoflurane metabolism, production of sevoflurane metabolites including inorganic fluoride and compound A, interactions of sevoflurane with neuromuscular blocking drugs, characteristics of sevoflurane for induction and emergence in special patient populations, clinical comparisons of sevoflurane with other general anesthetics. None of these studies adds significantly to the draft label currently under consideration by the Anesthesia Advisory Committee.

**Serious Adverse Events Not Addressed in Lable. None****Post Marketing Adverse Events:**

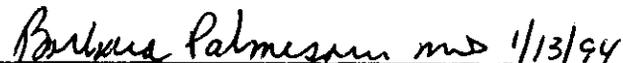
Transient hepatic injury in a patient anesthetized with sevoflurane. (Omori H, et al: J Jpn Soc Clin Anesth 1994;14:68-71) One report of malignant hyperthermia associated with use of succinylcholine and sevoflurane. Both of these complications are addressed in the current draft lable.

**Conclusions:**

The only studies which are not addressed in the draft label pertain to the effects of sevoflurane on the EEG. These effects are similar to those of other halogenated hydrocarbon anesthetics and do not raise any safety concerns such as risks for patients with epilepsy. Ultimately, information on EEG and cerebral blood flow and metabolism will need to be added to the label, but it is not critical for approval at this time.

Orig NDA # 20-478  
HFD-007/Div File  
HFD-007/RBedford  
HFD-007/  
HFD-502  
HFD-340  
F/T by

  
Robert F. Bedford, MD

 1/13/94  
Peer Reviewer

March 22, 1995

**MEDICAL OFFICER REVIEW  
PILOT DRUG EVALUATION STAFF**

**NDA #:** 20-478  
**Drug:** Sevoflurane (Sevorane): Review of Safety Update to Pending  
NDA submitted July 11, 1994  
**Sponsor:** Abbott Laboratories  
Abbott Park, IL 60064  
**Sponsor's Letter Dated:** March 8, 1995  
**Reviewer:** Robert F. Bedford, M.D., Medical Officer.  
**Review Date:** March 22, 1995  
**Submission Type:** Additional Safety Report  
**CSO:** Leslie Vaccari

**Resume and Background**

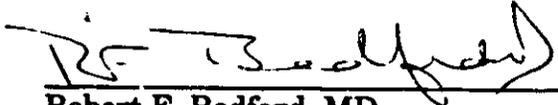
Sevoflurane is a new inhalational general anesthetic under NDA review. This report was submitted as an amendment to the sponsor's safety update of Nov 21, 1994. It gives a description of a case occurring in Sweden.

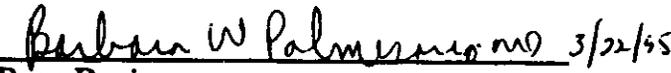
**Clinical Case:** A previously healthy 32 year old man with no prior history of neurological disorder underwent an uncomplicated sevoflurane general anesthetic as part of a company-sponsored protocol. Approximately 15 min after awakening in the recovery room he was observed to lose consciousness and develop symmetrical myoclonic movements lasting approximately 5 sec and occurring every 3-5 min for about 2.5 hr. The patient was unresponsive during this time, but had normal vital signs and EEG. The episode was broken with a sleep dose of thiopental and the patient awoke without neurologic compromise. The following day the patient sustained another similar episode lasting about 60 min and ending spontaneously.

**Comment re: Draft Label.** The current draft label lists movement, agitation and somnolence as adverse drug reactions possibly or probably related to sevoflurane. Given the presence of a normal EEG pattern and the uneventful awakening after this episode of somnolence and myoclonus, there is probably no change required in the label at this time.

**Conclusions:** This is an unusual reaction that might or might not be related to sevofluane. Similar episodes have been noted after other general anesthetics. Given the uneventful recovery, there is probably no regulatory action required at this time.

Orig NDA # 20-478  
HFD-007/Div File  
HFD-007/RBedford  
HFD-007/  
HFD-502  
HFD-340  
F/T by

  
Robert F. Bedford, MD

 3/22/85  
Peer Reviewer

DEC 8 1994

## Statistical Review and Evaluation

**NDA - 20,478**

**Name of Drug: Sevoflurane**

**Applicant: Abbott Laboratories**

**Indications: For induction and maintenance of general  
anesthesia in adult and pediatric patients  
surgery**

**Documents Reviewed: Vols. 2.42, 2.61, 2.122, 2.137, 2.159,  
2.201, 2.224, and 2.244 to 2.259  
dated 7/13/94 by CDER and an un-numbered  
volume of data diskettes of NDA 20,478 ,  
dated 9/2/94 by CDER.**

**Reviewer: Hoi M. Leung, Ph.D.**

**Date of Completed Review : 12/7/94**

### I. Introduction

There were over 40 clinical trials in this submission to demonstrate the safety and efficacy of sevoflurane in a variety of patient populations and surgical procedures. The number of patients in each study ranged from a few to over 500 and some of these studies are still on-going. This review evaluates the statistical methodology used by the sponsor in sevoflurane and examines the results from a representative sample of control clinical trials submitted in this NDA. The chosen studies are those with a large sample size within each type of patient populations so that estimates of parameters would be more precise than from studies with small sample size. No studies were reviewed in the neurosurgery patient population because the largest study had only 10 patients per treatment. For descriptions and results of these and other studies, the reader should consult the medical reviews. The following studies will be reviewed:

Adult : #10/SEVO 92-003 (n=555),  
          #11/SEVO 92-009(n=186)  
Pediatric: #21/SEVO 92-007 (n=525),  
          #23/SEVO 92-008(n=428)  
Cardiac: #20/SEVO 92-010 (n=273)  
Elderly: #32/SEVO 92-012 (n=126)  
Muscle Relaxants: #40/SEVO 92-013 (n=98)

### II. Statistical Methodologies

The sponsor's general approach in this submission was to use the analysis of variance (ANOVA) in continuous variables and the Fisher's Exact test or the Cochran-Mantel-Haenszel (CMH) method in binomial or ordered categorical data. A one-way (treatment) ANOVA was used in continuous

variables to compare sevoflurane with the active control if the study was a single-center study and a two-way ANOVA was used in multicenter studies with factors treatment, investigator, and their interaction. Many of the continuous variables such as induction, intubation, extubation, emergence, response to commands, first post-anesthesia analgesic, etc., were of the time to an event nature. There were a few outliers in these time to event variables because some patients required extensive surgical procedures which typically extended the time to recovery. The sponsor also investigated several alternative methods of analyses, such as trimmed means and nonparametric analysis and concluded that these alternative analyses were consistent with the protocol defined ANOVA approach. The Fisher's Exact test was used mainly in variables of binomial outcomes such as success or failure, e.g., in rate of induction success and emergence success as well as in the evaluation of adverse events. The determination of the Minimum Alveolar Concentration (MAC) for sevoflurane was made by logistic regression using sevoflurane concentration (%) and log-transformed age as independent variables. For small sample sizes, the Dixon Up-and-Down Method (JASA 1965; 60:967) was used instead. All statistical tests were 2-sided with  $p=.05$  as the level of statistical significance.

The sponsor's statistical methods are acceptable. An alternative method of analysis in the time to event variables is to use the survival analysis technique which will automatically handle the problem of outliers.

### III. Study 10 (SEVO 92-003)

This was a phase III, 12-center (7 in U.S. and 5 in Europe), open-label, randomized, study evaluating the effect of sevoflurane and isoflurane in the maintenance of anesthesia in adult ASA Class I, II, and III patients. The primary efficacy variables were Emergence Time, Recovery Time, Emergence Success, Maintenance Success, and Serum Fluoride levels.

The planned sample size was 400 patients with 200 patients in each treatment. In the actual study, 591 patients were enrolled and 587 patients were randomized. Of the 587 randomized patients, 555 (sevo 272 - 49% and iso 283 - 51%) patients were treated. There were only three patients (sevo 2; iso 1) discontinued prematurely due to adverse reactions. It is obvious that the study was overpowered by enrolling substantially more patients than the planned sample size. Demographics were well-balanced between treatment groups. Primary diagnosis was generally balanced also. There was a slight imbalance (not statistically significant) in surgical procedures in musculoskeletal system (sevo 39% vs. iso 31%) and nervous system (sevo 4% vs, iso 8%). There was no significant

difference in duration of surgery between treatments. Study drug concentration (MAC) during the entire anesthetic period was significantly lower in sevoflurane than in isoflurane (sevo: mean 0.57, s.e. 0.012 vs, iso: mean 0.72, s.e. 0.012). However, there were also significant investigator effect and treatment by investigator interaction. The interaction was of the quantitative nature which would still allow interpretation of the pooled data. There was no significant difference in the duration of study drug administration. Mean MAC hours of anesthesia was significantly lower in sevoflurane than in isoflurane (1.27 vs. 1.58).

### **Efficacy**

Results of the primary efficacy variables showed that Emergence, Response to Commands, and Orientation were significantly shorter for sevoflurane patients than for isoflurane patients. The average difference between treatment groups was about 5 minutes in these variables. However, there was no statistically significant difference in time to eligibility for recovery area discharge between treatments (sevo: mean 139.2, s.e. 15.6 vs. iso: mean 165.9, s.e. 16.3). The change from baseline in the Digit Symbol Substitution Test was significantly smaller in sevoflurane patients than in isoflurane patients. However only 25 patients were given this test and they were all from one investigator (Andeen). There were no statistically significant differences in induction success rate (sevo 92% vs iso 91%), maintenance success rate (sevo 89% vs. iso 88%), and emergence success rate (sevo 55% vs. iso 48%). The difference in overall success rate (sevo 48% vs. iso 39%) was statistically significant ( $p=.048$ ). However, this p-value was not adjusted for multiple endpoints. When multiple endpoints are considered, the result would not be significant.

### **Safety**

There was no significant difference in overall ADR rate (sevo 95% vs. iso 92%) and by body system. The most common ADRs were associated with the nervous (somnolence and dizziness) and digestive (nausea and vomiting) systems (55% each). Eleven patients in each group had severe ADRs considered to be drug related. Three sevoflurane patients had serum inorganic fluoride concentrations greater than 50  $\mu\text{M}$  but the elevated concentrations were transient and did not affect renal function.

### **Conclusions**

The lack of significant differences between treatments in this large study provides substantial evidence that

sevoflurane is as efficacious and safe as isoflurane in the study population.

#### IV. Study 11 (SEVO 92-009)

This was a phase III, 4-center (3 in U.S and 1 in Canada), open-label, randomized, active control study comparing the effect of sevoflurane and propofol in the induction and maintenance of anesthesia in adult ASA class I and II inpatients who underwent surgical procedures of an anticipated duration of 1 to 3 hours. The primary efficacy variables are induction time, induction success, emergence time, recovery time, recovery success, and maintenance success.

The planned sample size was 150 patients (75 per treatment). The sample size was not based on statistical power considerations but was adequate in this type of study to detect even a small difference in continuous variables. Of the 194 patients randomized into the study, 186 (93 in each treatment group) patients were administered study drug. One patient in each treatment group discontinued prematurely. Demographic variables were well-balanced between treatment groups. Females accounted for approximately 60% and Caucasian 85% of the population. The mean age was 43 years old. Primary diagnosis was generally similar between treatment groups with musculoskeletal and connective tissue (30%) the most common diagnosis. There was a slight imbalance (not statistically significant) in surgical procedures in digestive system (sevo 20% vs. propofol 31%) and female genital system (sevo 22% vs. propofol 12%). There was no significant difference in duration of surgery between treatments. Study drug concentration cannot be compared since sevoflurane was administered by inhalation while propofol was given by infusion. However, there was no significant difference in the duration of study drug administration between treatment groups. The average was about 132 minutes.

#### Efficacy

Results of the primary efficacy variables showed that Emergence, Response to Commands, and Orientation were significantly shorter for sevoflurane patients than for propofol patients. The average difference between treatment groups was between 3 to 5 minutes in these variables. There was also a significant qualitative treatment by investigator interaction in the variable Time to Emergence. This interaction was caused by the opposite result of one investigator (Blanck) compared to the other 3 investigators. Sevoflurane patients from investigator Blanck had longer mean emergence time than propofol patients while the other 3 investigators had opposite results. Even within the other 3 investigators whose sevoflurane patients had shorter time to

emergence, there was a large difference among them. However, there was no statistically significant difference in time to eligibility for recovery area discharge between treatments (sevo: mean 148.4, s.e. 8.9 vs. propofol: mean 141.4, s.e. 8.9). There were no statistically significant differences in induction success rate (sevo 77% vs. propofol 80%), maintenance success rate (sevo 89% vs. propofol 86%), emergence success rate (sevo 65% vs. propofol 66%) and overall success rate (sevo 42% vs. propofol 46%).

### **Safety**

There was no significant difference in the overall ADR rate (sevo 96% vs. propofol 87%). There was a statistically significant difference in adverse experience associated with the body as a whole (sevo 36% vs. propofol 54%). There was no other significant difference by body system. The most common ADRs were associated with the nervous (somnolence and dizziness) and digestive (nausea and vomiting) systems (approximately 55% each). Overall, 86% of the sevoflurane patients and 75% of the propofol patients experienced drug-related adverse events. Most of these ADRs were considered to be mild and moderate. Ten sevoflurane patients and 5 propofol patients had severe ADRs considered to be drug related.

### **Conclusions**

Sevoflurane was as effective as propofol for the induction and maintenance of anesthesia in adult ASA Class I and II inpatients. Sevoflurane patients had significantly shorter time to extubation, response to commands and orientation while propofol patients had significantly shorter time to induction and incubation. The comparison in time to emergence is somewhat problematic because of the qualitative treatment by investigator interaction. There was generally no significant difference in adverse reactions between sevoflurane and propofol patients. However, severe adverse reactions that were considered to be drug-related were numerically higher in sevoflurane than in propofol patients.

### **V. Study 21 (SEVO 92-007)**

This was a 13-center (5 U.S. and 8 European) open-label randomized, active control study comparing the effect of sevoflurane and halothane in the induction and maintenance of anesthesia in pediatric ASA Class I and II outpatients with an anticipated duration of surgical procedures up to 3 hours. The primary efficacy variables are identical to those in Study 11 above. There were 7 amendments to the original protocol. Three amendments applied to all sites while the other four amendments were site specific. The amendments that were site specific were generally criteria

that limited the inclusion and exclusion of patients who could enter the study.

The planned sample size was 400 patients with 200 patients in each treatment. This was based on a statistical power (0.80 and alpha level of 0.05) consideration to detect a 10% difference between halothane and sevoflurane in the mean recovery time. In the actual study, 530 patients were enrolled and randomized. Of the 530 randomized patients, 525 (sevo 268 - 51% and halo 257 - 49%) patients were treated. One patient in each group discontinued prematurely due to adverse reactions. It is obvious that the study was overpowered by enrolling substantially more patients than the planned sample size. Demographics were balanced between treatment groups. Seventy-four percent of all patients were male and 91% of all patients were ASA Class I. Primary diagnosis and surgical procedure were well-balanced between the two treatments. The most common surgical procedures were associated with the digestive system (24%), "nose, mouth, pharynx" (21%) and male genital system (19%). There was no significant difference in duration of surgery (mean 31.5 minutes) between treatments. Although the average concentration of study drug during the anesthetic period was significantly lower in the sevoflurane patients than in the halothane patients, there was also significant treatment by investigator interaction. Among the 13 investigators, 10 had sevoflurane concentration lower than that of halothane; two had sevoflurane concentration higher than that of halothane and one had equal concentration between the two treatments. There was no significant difference in duration of study drug administration between treatment groups. The average duration was about 54 minutes.

### **Efficacy**

Results of the primary efficacy variables showed that Emergence and Response to Commands were significantly shorter for sevoflurane patients than for halothane patients. The average difference between treatment groups was between 7.5 to 8.5 minutes in these two variables. However, there was no statistically significant difference in Orientation and Time to Eligibility for Recovery Area Discharge between treatments. Induction, intubation, and extubation were also significantly shorter for sevoflurane patients than for halothane patients. There were no statistically significant differences in induction success rate (sevo 61% vs. halothane 63%), maintenance success rate (sevo 91% vs. halothane 90%), emergence success rate (sevo 55% vs. halothane 58%) and overall success rate (sevo 39% vs. halothane 41%).

## Safety

There was no significant difference in the overall ADR rate (sevo 77% vs. halothane 78%). There was a statistically significant difference in adverse experience associated with the nervous system (sevo 41% vs. halothane 30%). Within the nervous system, agitation occurred significantly higher in the sevoflurane group (31%) than in the halothane group (18%). There was no other significant difference by body system. The most common ADRs were associated with the respiratory (sevo 46% vs. halo 49%) system. The most common adverse experience within the respiratory system was increased cough (sevo 33% vs. halo 39%). Overall, 65% of the sevoflurane patients and 69% of the halothane patients experienced drug-related adverse events. Most ADRs were considered to be mild or moderate. Although there was no significant difference between treatments in the drug related adverse experience in the cardiovascular system as a whole, within the cardiovascular system there were significant differences in tachycardia (sevo 19 vs. halo 7), arrhythmia (sevo 1 vs. halo 10), and bradycardia (sevo 1 vs. halo 8). Eighteen (18) sevoflurane patients (mostly agitation and/or apnea) and 11 halothane patients (mostly agitation, nausea, or increased cough) had severe ADRs considered to be drug related. Interpretation of Laboratory and chemistry measurements is somewhat problematic because of missing values from many patients. The missing values ranged from 20 to 40% of the patients depending on the parameters measured. Also, there were more missing data in the laboratory measurements in the halothane patients than in the sevoflurane patients.

## Conclusions

Sevoflurane is effective in the induction and maintenance of anesthesia in pediatric inpatient surgery. It generally has shorter times to extubation, emergence, and response to commands than halothane. There were no significant differences in the success rates of induction, maintenance, and emergence. There was significantly more respiratory adverse experiences in sevoflurane patients than in halothane patients. Although there was no significant difference in cardiovascular system, significantly more halothane patients had arrhythmia and bradycardia than sevoflurane patients while the opposite was the case for tachycardia. There were also more drug-related severe adverse reactions associated with sevoflurane than with halothane in this study.

## **VI. Study 23 (SEVO 92-008)**

This was a 12-center (6 U.S. and 6 European) open-label randomized, active control study comparing the effect of sevoflurane and halothane in the induction and maintenance of anesthesia in pediatric ASA Class I and II inpatients with an anticipated duration of surgical procedures of at least one hour. The primary efficacy variables are identical to those in Study 21 above. In addition, at least 25% of all clinically evaluable patients had serum inorganic fluoride level determinations at specific time points prior to and following anesthesia.

The planned sample size was 400 patients with 200 patients in each treatment. This was based on a statistical power (0.80 and alpha level of 0.05) consideration to detect a 20% difference between halothane and sevoflurane in the mean emergence time. In the actual study, 432 patients were enrolled and 430 of them were randomized. Of the 430 randomized patients, 428 (214 in each group) patients were treated. Two sevoflurane patients and 3 halothane patients discontinued during the intra-operating period.

Demographics were balanced between treatment groups. Sixty-one percent of all patients were male and 63% of all patients were ASA Class I. The mean age was 6.5 years old. Primary diagnosis and surgical procedure were well-balanced between the two treatments. The most common surgical procedures were associated with "nose, mouth, pharynx" (31%) and musculoskeletal system (25%). There was no significant difference in duration of surgery (mean 93.3 minutes) between treatments. There were no significant differences in the average concentration (0.87 s.e. .02) of study drug during the anesthetic period and the duration of study drug administration (mean 130 minutes s.e. 6.4). However, there was significant difference among investigators.

### **Efficacy**

Induction and extubation were significantly shorter for sevoflurane patients than for halothane patients. For the primary efficacy variables, Emergence and Response to Commands were significantly shorter for sevoflurane patients than for halothane patients. The average difference between treatment groups was between 3.5 to 4.3 minutes in these two variables. There were no statistically significant differences in induction success rate (sevo 58% vs. halothane 49%), maintenance success rate (sevo 91% vs. halothane 92%), emergence success rate (sevo 42% vs. halothane 34%) and overall success rate (sevo 27% vs. halothane 19%).

## Safety

There was no significant difference in the overall ADR rate (sevo 91% vs. halothane 92%) and for any body systems. The most common ADRs were associated with the respiratory (sevo 60% vs. halo 60%) system. The most common adverse experience within the respiratory system was increased cough (sevo 45% vs. halo 53%). Overall, 78% of the sevoflurane patients and 85% of the halothane patients experienced drug-related adverse events. Most of these ADRs were considered to be mild or moderate. A significant difference was observed between the two treatments for the incidence of study drug-related digestive system adverse experiences (sevo 35% vs. halo 48%). Vomiting was the most common ADR within the digestive system (sevo 31% vs. halo 40% NS). Although there was no significant difference between treatments in the drug-related adverse experience in the cardiovascular system, within the cardiovascular system there were significant differences in tachycardia (sevo 16 vs. halo 4 patients) and bradycardia (sevo 5 vs. halo 25 patients). The most common study drug-related adverse experiences were those associated with the nervous system (sevo 46% vs. halo 48%). Eighteen (18) sevoflurane patients (mostly agitation or nausea) and 27 halothane patients (mostly agitation, nausea, or increased cough) had severe ADRs considered to be drug related. Missing values were about 10% for most of the laboratory measurements.

## Conclusions

Sevoflurane is effective in the induction and maintenance of anesthesia in pediatric inpatient surgery. Similar to Study 21, it generally has shorter times to extubation, emergence, and response to commands than halothane. There were no significant differences in the success rates of induction, maintenance, and emergence. Safety profile was also similar to that of Study 21 except that contrary to Study 21, there were fewer drug-related severe adverse reactions associated with sevoflurane than with halothane in this study.

## VII. Study 26 (SEVO 92-010)

This was a Phase III, 13-center (9 U.S., 1 Canada, 3 European), open-label, randomized, active control study comparing sevoflurane with isoflurane as an adjunct with narcotics in adult ASA Class II, III, and IV inpatients who underwent elective coronary artery bypass graft (CABG) surgery. The primary efficacy variables are the incidence of pre-cardiopulmonary bypass myocardial ischemia and maintenance success. Secondary efficacy variables include cardiac deaths, myocardial infarction and ventricular failure.

The planned sample size was a total of 280 patients (140 in each treatment). This was based on the assumption that the incidence of pre-CPB ischemia in the isoflurane group would be 15%. The said sample size would have a power of 0.8 ( $\alpha = 0.05$ ) to detect a difference of 15% between treatment groups. Thus the planned sample size could only detect a two-fold increase in incidence of ischemia. In the actual study, 287 patients were enrolled and 284 of them were randomized. A total of 273 patients (sevo 140 & iso 133) were treated and 268 of them completed the study. Demographics, ASA Class, and cardiovascular classifications were well-balanced between treatment groups. The majority of the patients were male (85%), Caucasian (96%), ASA Class III (72%) with a mean age of 60 years old. Significantly more sevoflurane patients (14%) had a cardiovascular history of significant arrhythmia than isoflurane patients (5%). Duration of surgery (232 minutes, s.e. 5.3), study drug concentration (0.51, s.e. .019), and duration of study drug administration (112 minutes, s.e. 3.63), MAC hours (0.96 s.e. .046) were very much comparable between the two treatment groups.

### **Efficacy**

Of the 272 evaluable patients, 32 patients (sevo 15 and iso 17) did not have readable Holter monitoring time. This casts some doubt on the quality of the Holtering monitoring data. There was no statistically significant difference in frequency of ischemic events between treatment groups either before induction (sevo 12% vs. iso 13%) or between induction to onset of CPB (sevo 7% vs. iso 11%). This is to be expected due to the planned sample size and the further reduction of sample size from unreadable Holter monitoring time. There was also no significant difference in duration of ischemic events between sevoflurane and isoflurane. Maintenance success rate was comparable between treatment groups (sevo 94% vs. iso 92%) as was induction success rate (91% both) and overall success rate (sevo 86% vs. iso 84%). There were no statistically significant differences in any of the secondary efficacy variables.

### **Safety**

There was no significant difference in the overall ADR rate (sevo 76% vs. iso 81%) and for any body systems. The most common ADRs were associated with the cardiovascular (both 66%) system. The most common adverse experience within the cardiovascular system was hypotension (sevo 26% vs. iso 32%), hypertension (sevo 26% vs. iso 22%), and atrial fibrillation (sevo 26% vs. iso 21%). Overall, 29% of the sevoflurane patients and 30% of the isoflurane patients experienced drug-related adverse events. Most of these ADRs were considered to be mild or moderate. The most common

study drug-related adverse experiences were those associated with the cardiovascular system (sevo 18% vs. iso 19%).

### Conclusions

The Holter monitoring was the key to the measurement of the primary efficacy variable, frequency of pre-CPB myocardial ischemia. Twelve (12%) percent of the Holter monitoring data was classified as unreadable. This casts some doubt as to the quality of the Holter monitoring data. The observed frequency of pre-CPB myocardial ischemia was low. Thus, if there were some cases of myocardial ischemia among those unreadable Holter monitoring data, the conclusions could be affected. Taking the data at face value, this study shows that sevoflurane and isoflurane behaved very much the same as an adjunct with narcotics prior to cardiopulmonary bypass surgery in adult patients.

### VIII. Study 32 (SEVO 92-012)

This was a Phase III, 6-center (U.S.), open-label, randomized, active control study comparing sevoflurane and isoflurane in elderly (age 65 or higher) ASA Class I, II, and III inpatients who underwent surgical procedures of an anticipated duration of up to 3 hours. The primary efficacy variables are Emergence time, Maintenance Success, Recovery time and Success. Serum inorganic fluoride concentrations were measured at 5 sites.

The planned sample size was 100 patients which was not based on statistical power considerations. In this study, 136 patients were enrolled and 132 of them were randomized. A total of 126 patients (sevo 62 & iso 64) were treated and 124 of them completed the study. Demographics and ASA Class were comparable between treatment groups. The majority of the patients were male (67%), Caucasian (90%), ASA Class II and III (55% and 43%) with a mean age of 72 years old. The most common primary diagnosis was in musculoskeletal system and neoplasms which were comparable between treatments. However, significantly more sevoflurane patients (23%) than isoflurane patients (6%) had a primary diagnosis in the digestive system. Duration of surgery (143 minutes, s.e. 16), study drug concentration (0.52, s.e. .033), and duration of study drug administration (173 minutes, s.e. 16), MAC hours (1.52 s.e. .017) were not significantly different between the two treatment groups.

### Efficacy

There were no statistically significant differences between the two treatments in any of the primary efficacy variables. Emergence and Response to Commands were numerically shorter for sevoflurane patients than for isoflurane patients. The average difference between

treatment groups was 3.2 and 4.6 minutes in these two variables, respectively. The sample size was too small to detect this magnitude of difference. The difference would have been statistically significant had the sample size been tripled as demonstrated in Study 23. The induction success rate was 60% for sevoflurane and 44% for isoflurane. The maintenance success rate (sevo 71% vs. iso 73%), emergence success rate (sevo 80% vs. iso 78%) and overall success rate (sevo 38% vs. iso 22%) between treatment groups were also not statistically significant.

### **Safety**

There was no significant difference in the overall ADR rate (sevo 87% vs. iso 92%) and for any body systems. The most common ADRs were associated with the cardiovascular (sevo 63% vs. iso 75%) system. The most common adverse experience within the cardiovascular system was hypotension (sevo 37% vs. iso 52%) and hypertension (sevo 34% vs. iso 28%). Overall, 57% of the sevoflurane patients and 72% of the isoflurane patients experienced drug-related adverse events. Most of these ADRs were considered to be mild or moderate. The most common study drug-related adverse experiences were those associated with the cardiovascular system (sevo 39% vs. iso 53%). There were more isoflurane patients experienced drug-related incidence of nausea (sevo 18% vs. iso 31%) and vomiting (sevo 5% vs. iso 19%). Two patients had serum inorganic fluoride concentrations greater than 50 uM with no evidence of renal damage.

### **Conclusions**

The sample size of this study was too small to detect the magnitudes of differences similarly observed in other studies both in efficacy and safety. However, the mean times to most of the primary efficacy variables were numerically shorter than those of isoflurane which were consistent with other studies. The safety profile of sevoflurane was also comparable to that of isoflurane.

### **IX. Study 40 (SEVO 92-013)**

This was a Phase II, single center (Netherlands), open-label, randomized, active control study comparing the potentiating effect of sevoflurane and isoflurane on muscle relaxants (vecuronium, pancuronium, and atracurium) in adult ASA Class I and II inpatients. Within each of the three muscle relaxant groups, patients were randomly assigned to receive sevoflurane + alfentanil, isoflurane + alfentanil, or alfentanil alone, as their primary anesthetic agent (with nitrous oxide/oxygen) during the anesthetic maintenance period. Neuromuscular function was assessed by mechanomyogram (MMG) and electromyogram (EMG). Secondary efficacy variables included recovery parameters which were

similar to those used in the other studies discussed previously.

Of the 102 patients enrolled, 101 were randomized and 98 of them were treated. Eight patients were excluded from the efficacy analysis because the initial dose of muscle relaxant provided complete muscle relaxation, prohibiting the establishment of a dose response. The remaining 90 patients were distributed equally among the 9 cells (3 muscle relaxants by 3 treatments : 10 patients per cell). Fifty percent of the patients were males and about 90% of the patients were classified as ASA Class I. Demographics among treatment groups within each muscle relaxant category were not statistically significant except for the tobacco use history within the alfentanil group (significantly more tobacco users) in the atracurium category. Since the sample size in each cell was only 10, it would be difficult to compare statistically whether there was any significant difference among treatments within a muscle relaxant. Duration of surgery was the shortest (mean 85 minutes s.e. 12.7) with atracurium, followed by vecuronium (mean 134 s.e. 27), and pancuronium (mean 171 minutes s.e. 31.7).

#### **Efficacy**

There were no statistically significant differences between sevoflurane + alfentanil and isoflurane + alfentanil within each of the 3 muscle relaxant categories in any of the primary efficacy variables. Their mean values were numerically close also. The alfentanil alone group was quite different from the other two treatments. Most pairwise comparisons between alfentanil alone and the other two treatments resulted in statistically significant differences. For the secondary efficacy variables, the pooled analysis of all muscle relaxants categories resulted in statistically significant differences between sevoflurane + alfentanil and isoflurane + alfentanil in emergence, response to commands and orientation. Sevoflurane patients had shorter time in each of the three comparisons. However, there were no significant differences between sevoflurane + alfentanil and alfentanil alone in any of the recovery parameters. Strangely, the various success rates (induction, maintenance, emergence, and overall) showed that sevoflurane + alfentanil had the lowest success rates among the three treatment groups with a statistically significant difference in the maintenance success rate.

#### **Safety**

There was no significant difference in the overall ADR rate (sevo + alf 91% vs. iso + alf 91% vs. alf 81%). There was a statistically significant difference in the cardiovascular system (sevo +alf 44% vs. iso+alf 12% vs. alf 16%). The most common ADRs were associated with the

digestive (sevo+alf 69% vs. iso+alf 68% vs. alf 56%) system. Overall, 81%, 56%, and 69% of the sevoflurane + alfentanil, isoflurane + alfentanil, and alfentanil patients, respectively experienced drug-related adverse events. This difference was significant between sevoflurane + alfentanil and isoflurane + alfentanil. Most of these ADRs were considered to be mild or moderate. The most common study drug-related adverse experiences were those associated with the digestive and cardiovascular systems. There were significantly more sevoflurane + alfentanil patients than isoflurane + alfentanil or alfentanil alone patients experienced drug-related incidence of hypotension (sevo+alf 38% vs. iso+alf 3% vs. alf 3% ) and chills (sevo+alf 25% vs. iso+alf 6% vs. alf 3%).

### Conclusions

This was a Phase II study investigating the potentiating effect of sevoflurane with different muscal relaxants. The sample size was small resulting in inconclusive comparisons with isoflurane. However, at least for the primary efficacy variables MMG and EMG, sevoflurane + alfentanil behaved very much like isoflurane + alfentanil in each of the three muscle relaxants. On the other hand, sevoflurane + alfentanil patients generally experienced more hypotensions and chills. A definitive comparison will require a larger sample size in a Phase III study setting.

### X. Overall Conclusions

The statistical methods are generally acceptable. A consistent analysis approach was used throughout the application. A caution is in order in interpreting the statistically significant findings from individual studies. Since there were large number of variables tested at multiple time points from many studies and all the stated p-values were nominal p-values unadjusted for multiple comparisons, occasional significant results by chance alone are unavoidable. It is advisable to see if a significant result is replicated in similar studies before drawing conclusions. Also, the large sample sizes in many of these studies have high power to detect a very small difference between treatments. Thus, clinical significant difference is important in judging a statistically significant finding.

Based on the results of the seven studies reviewed here, it is clear that sevoflurane is effective in adult and pediatric patient population compared to isoflurane and propofol for adults and halothane for pediatrics when used for induction and maintenance of general anesthesia. There was consistent evidence that sevoflurane had shorter recovery times than its comparators. However, this could be due to the lower concentrations used in sevoflurane. There was also a lack of information of the comparability in the

depth of anesthesia between treatment groups. There was essentially no difference in the success rates of recovery parameters between sevoflurane and its comparators. The safety profile was generally similar to that of isoflurane or halothane in terms of adverse experiences. There may be some differences in adverse reactions from individual studies, but such differences were not consistent across studies. There were a few patients who had serum inorganic fluoride above 50 uM in those studies where serum inorganic fluoride level was measured. However, this seemed to be a transient effect. In the cardiac surgery of elderly patients, the study was somewhat tarnished by the quality of the Holter monitoring data in which 12% of the data was unreadable. Since the incidence of ischemia from the readable data was low, any potential ischemia incidence from the unreadable data could alter the findings of the study. For the muscle relaxants study, the sample size was too small to draw a definitive conclusion though sevoflurane behaved similarly to isoflurane in the presence of three kinds of muscle relaxants.

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Peer Reviewer:

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NDA 20-478  
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VACCARI

MAR 3 1995

**COVERING MEMORANDUM FOR NDA No 20-478**

Sevoflurane<sup>®</sup>  
Inhalational anesthetic agent

NDA No. 20-478

Abbot Laboratories  
One Abbot Park Road,  
D389, AP30  
Abbot Park  
Illinois, 60064

Reviewer: Peter Lockwood, MSc.

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The number of pages of this NDA review complete with Appendices, approximates 700. Due to this voluminosity, only the review itself without the Appendices is circulated. A copy of the review, complete with appendices is filed in the Division of Biopharmaceutics, Drug and Chronological files.

Sevoflurane<sup>®</sup>  
Inhalational anesthetic agent

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Abbot Laboratories  
One Abbot Park Road, D389,  
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Illinois, 60064

Reviewer: Peter Lockwood, MSc.  
Review Date:  
October 7, 1994

Submission Date:  
January 7, 1994

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## REVIEW OF SEVOFLURANE PHARMACOKINETICS

### 1 BACKGROUND

This submission seeks approval for Sevoflurane which is a fluorinated derivative of methyl isopropyl ether (fluoromethyl-2,2,2-trifluoro-1-{trifluoromethyl}-ethylether) an inhalational anaesthetic. The product was initially developed for clinical use by Maruishi Pharmaceutical Co., Osaka, Japan and the product was approved for marketing in Japan in January 1990. Clinical development in the United States was subsequently undertaken by Maruishi in 1992. Maruishi initiated a licensing agreement with Abbot Laboratories under which Abbot Laboratories assumed responsibility for the worldwide clinical development of sevoflurane. The delineation of the pharmacokinetics of sevoflurane and its metabolites hexafluoroisopropanol (HFIP) and inorganic fluoride are based on the results of 12 studies assumed by Abbot (designated SEVO-xx-xxx) and 12 Abbot sponsored studies (designated SEVO-xx-xxx). There is some speculation that high fluoride ion blood concentrations may be nephrotoxic. This is based on reports that the bio-transformation product of a similar fluorinated agent (methoxy-flurane) is nephrotoxic.

### 2 OVERVIEW OF PHARMACOKINETIC ASSESSMENT OF INHALATIONAL ANESTHETICS.

In previous NDA submissions and refereed journals, the pharmacokinetics of an inhalational agent have been characterized by determining the rate of rise of the alveolar concentration to the inspired concentration ( $F_A/F_I$ ) with time (referred to as washin) or the rate of decline of the alveolar concentration during recovery from anaesthesia ( $F_A/F_{A0}$ ) (referred to as washout). In this submission, the sponsor has delineated the PK of this inhalational anesthetic via the analysis of venous blood concentration measurements and is the first sponsor to do so.

The delineation of the pharmacokinetics of a volatile anesthetic agent are complicated by the fact that it is difficult to quantify the dose of anesthetic administered to each patient, unless this is a particular study requirement. Patients are administered drug until a desired endpoint is reached (depth of anesthesia) and this endpoint is dependent on physiological (e.g. tidal volume, cardiac output, age), mechanical (e.g. flow rate, carrier gas or circuit volume) and pharmacodynamic variables (relationship between partial pressure of anesthetic in the brain and depth of

anesthesia). The physiological variables are never constant during induction or maintenance of anesthesia and therefore the dose must be adjusted accordingly during the course of surgery to maintain anesthesia at the desired depth. The consequence of this difficulty in quantifying the dose, is that pharmacokinetic parameters determined from the various studies in this submission cannot be interpreted with any real degree of confidence.

Furthermore, it could be argued that the sampling of venous blood is a poor choice of sampling compartment and poorly represents the partial pressure in arterial blood or the partial pressure of the anesthetic gas in the end-tidal gas. However, in a study conducted by Carpenter et al. (1989), where  $P_A$  (end-tidal partial pressure),  $P_a$  (arterial partial pressure) and  $P_v$  (venous partial pressure) were measured for isoflurane and halothane, it was demonstrated that both  $P_A$  and  $P_v$  correlated with  $P_a$ . The correlation was better for  $P_A$  ( $R=0.960$  vs  $0.878$ ) and there was less scatter in the data. When both  $P_A$  and  $P_v$  data were correlated with  $P_a$ , and  $P_v$  data were limited to highly arterialized venous samples<sup>1</sup>, (a-v  $O_2$  content difference less than 1 vol %), the R value improved to 0.945.  $P_A$  in general was more accurate for isoflurane. Thus, results of this study suggested that inaccuracies in pharmacokinetic parameter estimates arising from the choice of sampling at venous sites are likely to be minimal.

Cross-study comparisons of parameter estimates which are usually inherent in the course of any review are complicated for inhalational anesthetics, because as has already been alluded to, subjects in the study received different doses. Compounding this, is the fact that different anesthetic gas mixtures may be administered in different studies. For these reasons, less emphasis is placed on cross study comparisons in this review. Finally, for purposes of completeness a summary and review of the published and unpublished information on the disposition and metabolism of sevoflurane in animals is provided in Appendix 6.

### 3 SYNOPSIS

Twenty-four (24) studies were submitted in this NDA to delineate the pharmacokinetics of sevoflurane in patients and healthy volunteers. These studies were primarily safety and efficacy studies and included a few plasma concentration measurements although generally the studies were not designed as true pharmacokinetic studies. Three studies (SEVO 93-037, 520 & 522) conducted in healthy patients, measured blood concentrations of the parent drug while the remainder focused on measuring the concentrations of inorganic fluoride (a biotransformation product of sevoflurane). It has been reported that following administration of methoxyflurane, serum inorganic fluoride concentrations  $> 50\mu M^2$  were correlated with the development of vasopressin resistant, polyuric, renal failure<sup>37</sup>. In study SEVO 93-037, estimates of sevoflurane dose were made from inspiratory and expiratory sevoflurane vapor concentrations and minute ventilation. Dose estimates, in conjunction with quantities of the biotransformation

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<sup>1</sup> Cutaneous blood flow is greatly increased during anesthesia and direct arteriovenous shunts open in the hand such that venous blood in the forearm and hand is "arterialized" and the  $P_{CO_2}$  is nearly identical to that in arterial blood<sup>37</sup>.

<sup>3</sup> Throughout the course of the review, concentrations are expressed as  $\mu M$ . To describe sevoflurane and inorganic fluoride concentrations in terms of ng/ml, the conversion factors are as follows; sevoflurane -  $1\mu M = 2.25$  ng/mL; fluoride -  $1\mu M = 19$  ng/mL. (mw sevoflurane = 200.25, atomic wt inorganic fluoride = 19)

products (conjugated hexafluoroisopropanol (HFIP) and fluoride ion collected in the urine, permitted estimation of the percent of the total sevoflurane dose eliminated as metabolite (up to approximately 7%).

$C_{max}$ ,  $AUC_{0->t}$ <sup>3</sup>,  $AUC_{inf}$  and half-life for sevoflurane were determined in these three studies but displayed wide variability due to administration of sevoflurane for different durations and in different mixtures of carrier gas. Estimates of the half-life of sevoflurane in oxygen from blood measurements varied from between 0.81hr and 3.17hr. The 0.81 hour estimate probably reflects the dosage and sampling regimen. It is likely that insufficient samples were collected to capture the true terminal elimination phase in the studies which reported these lower values. In two studies (SEVO-93-037, -520) in which sevoflurane was administered with pure oxygen,  $C_{max}$  ranged from 345-1641  $\mu$ M. The mean  $C_{max}$  for both studies was 761 $\mu$ M and 716 $\mu$ M respectively. Maximum concentrations of sevoflurane were assumed to occur during or at the termination of the anesthetic administration.

The results of these studies suggest sevoflurane exhibits triphasic blood disposition pharmacokinetics although the sponsor concludes that sevoflurane exhibits biphasic blood disposition pharmacokinetics. A three compartment model is more consistent with what is reported in the literature.<sup>27</sup>

A second analysis based on a NONMEM (nonlinear mixed effects modeling) Bayesian POSTHOC approach was conducted by the sponsor. Individual parameter estimators were determined by a convolution technique. However in generating the individual parameter estimates, assumptions relative to the input rate function and disposition function were violated. Specifically the input rate was considered constant and the disposition function bi-exponential. The impact of this assumption violation is unclear and thus the outcome of this analysis is questionable.

In a study conducted in healthy subjects (the results of which have already published<sup>27</sup>) sevoflurane demonstrated a more rapid increase in  $F_a/F_i$  and more rapid decrease in  $F_a/F_{a_0}$  than isoflurane, where  $F_a$  is the alveolar (end-tidal) anesthetic concentration,  $F_i$  is the inspired concentration, and  $F_{a_0}$  is the last alveolar concentration prior to termination of anesthetic administration. These results are to be incorporated in the label but a report of this study was not included in the submission. Never-the-less, because some of the data contained within the publication was formally reviewed in a previous NDA (Desflurane NDA No) and assessed by a journal referee, the inclusion of the above-mentioned information in the label in the absence of any formal review by this reviewer is acceptable. This decision was endorsed by senior management from the FDA's Division of Biopharmaceutics.

The effects of sevoflurane on the displacement of drugs from serum and tissue proteins has not

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<sup>3</sup>  $AUC_{0->t}$  was computed using a linear trapezoidal rule from the start of anesthesia ( $t = 0$ ) to the time of the last sample for each patient.  $AUC_{0->t}$  was computed by division of the concentration at the last sampling time predicted by log-linear regression, by the terminal elimination rate constant.  $AUC_{0->inf}$  was the sum of  $AUC_{0->t}$  and  $AUC_{t->inf}$ .

been investigated. Other fluorinated volatile anesthetics have been shown to displace drugs from serum and tissue proteins in vitro. It is speculated that the displacement of highly bound drugs which have a low extraction ratio would have no clinical significance because these displaceable compounds have an extremely large unbound volume in which to distribute. Thus the change in the unbound blood concentration is likely to be minimal. There is a report however, of phenytoin intoxication in a child following halothane anesthesia', see Karlin and Kutt, 1970, J. Pediatr. 76, 941).

Gender was considered as a covariate in the analysis<sup>4</sup> of pharmacokinetic data obtained in study 520. Sevoflurane AUC's were observed to increase proportionally with dose for females but disproportionately for males. However due to the fact that the amount administered is governed by a pharmacodynamic endpoint (depth of anesthesia) and that accurate quantification of the dose administered is extremely difficult, the dose which is traditionally an independent variable now must be considered as a dependent variable. The consequence of this, is a much greater degree of variability observed within the data set and this confounds the drawing of meaningful conclusions. Thus no firm conclusions were drawn from the gender analysis.

As depicted in Appendix 5, sevoflurane is metabolized to HFIP with release of inorganic fluoride and CO<sub>2</sub>. Once formed HFIP is rapidly conjugated with glucuronic acid and eliminated as a urinary metabolite. Inorganic fluoride pharmacokinetic parameters following sevoflurane administration were determined in eight studies. Fluoride concentrations were measured after single, extended and repeat exposure to sevoflurane, in normal surgical and special patient populations including pediatric, elderly, renally-impaired and hepatically-impaired patients.<sup>1, 2, 5-10</sup> Collectively, these results suggest the elimination of fluoride is complex and not well understood. The studies indicate that peak fluoride concentrations are generally observed within 2 hours after termination of sevoflurane administration. In sixty healthy patients receiving sevoflurane in pure oxygen (mean 1.27 MAC; range 0.72-2.13) for 1-6 hours, peak concentrations ranged from 12-75 μM. Biphasic elimination was observed in up to 30% of adult patients. However, due to possible fluctuations in baseline fluoride concentrations, diurnal variation, pH effects etc., the observation of multiphasic fluoride disposition following sevoflurane administration must be interpreted with caution.

Dose proportionality of inorganic fluoride concentrations in blood following sevoflurane administration (3, 6, and 9 MAC-hr)<sup>4</sup> were assessed in healthy male subjects in Study SEVO-93-044 and Study -536.<sup>3, 4</sup> The results of these studies indicate that fluoride concentrations increase less than proportionally with increasing sevoflurane dose where dose was approximated as MAC-Hr. This suggests that either clearance is increasing with increasing doses or that fluoride production is capacity limited for doses greater than 3 MAC-hr. In contrast, in Study 531, fluoride ion production was shown to correlate with sevoflurane doses of lower MAC (0.54; 36%CV) and shorter duration (1.64hr, 84%CV).

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<sup>4</sup> MAC is defined as the minimum alveolar concentration, in percent, necessary to achieve a predefined depth of anesthesia. For sevoflurane this is 2.05% in adults. Thus 2.05% sevoflurane represents one MAC. MAC-hours (MAC-Hr) are defined as the average anesthetic concentration (in MAC units) multiplied by the duration (in hours) of anesthetic administration.

Repeat exposure (2nd and 3rd surgical procedures) were investigated by the sponsor (531) but the results were largely meaningless. The duration and MAC of the second exposure were generally greater than the first and varied extensively. Additionally the time between administrations varied extensively among subjects. As a consequence of these uncontrolled variables it was not possible to draw any firm conclusions regarding the kinetics of fluoride accumulation following repeated exposure, other than infer that the safety of the patients was not affected by fluoride ion concentrations following repeat exposure. The maximum fluoride ion concentrations observed all occurred in one patient following sequential exposures. These concentrations were  $81\mu\text{M}$ ,  $86\mu\text{M}$  &  $98\mu\text{M}$  at each exposure respectively.

Inorganic fluoride pharmacokinetics following sevoflurane administration were assessed in a number of studies involving special patient populations.<sup>13-22</sup> These include six studies in pediatric patients,<sup>13-18</sup> two studies in elderly patients,<sup>7,19</sup> two studies in patients with renal impairment,<sup>20,21</sup> one study in patients with hepatic impairment,<sup>22</sup> and one study in obese patients<sup>7</sup>.

Mean fluoride  $C_{\text{max}}$  values (range<sup>23</sup>  $12\text{-}21\mu\text{M}$ ) in pediatric patients were lower and half-life values were shorter ( $t_{1/2\text{ monophasic}}$  range<sup>23</sup>  $1.7\text{-}9.7\text{hrs}$ ) following sevoflurane administration, than those observed in adults ( $C_{\text{max}}$  range<sup>23</sup>  $25\text{-}45\mu\text{M}$ ,  $t_{1/2\text{ monophasic}}$  range<sup>23</sup>  $9\text{-}15\text{hrs}$ ). Mean fluoride  $\text{AUC}_{0-\infty}$  and dose-normalized  $\text{AUC}_{0-\infty}$  values were significantly greater in elderly ( $\geq 65$  years) patients following sevoflurane administration compared to a younger adult population (mean  $\text{AUC}_{0-\infty}$  elderly  $781\mu\text{M}\cdot\text{hr}$ , mean  $\text{AUC}_{0-\infty}$  young  $474\mu\text{M}\cdot\text{hr}$ ); however,  $C_{\text{max}}$ ,  $T_{\text{max}}$ , and half-life were not significantly different (mean  $C_{\text{max}}$  elderly  $25.6\mu\text{M}$ , young  $24.7\mu\text{M}$ ; mean  $t_{1/2\text{ monophasic}}$  elderly  $15.5\text{hrs}$ , mean  $t_{1/2\text{ monophasic}}$  young  $15.4\text{hrs}$ ; mean  $t_{1/2\text{ biphasic}}$  elderly  $24.4\text{hrs}$ , mean  $t_{1/2\text{ biphasic}}$  young  $23.2\text{hrs}$ ). Fluoride half-life was significantly prolonged in patients with renal impairment (mean  $t_{1/2\text{ monophasic}}$   $35\text{hrs}$ ; range  $15\text{-}61\text{hrs}$ ) with accompanying increases in  $\text{AUC}_{0-\infty}$  (mean  $\text{AUC}_{0-\infty}$   $1072\mu\text{M}\cdot\text{hr}$ ) and dose-normalized  $\text{AUC}_{0-\infty}$  (mean  $\text{AUC}_{0-\infty}/\text{dose}$   $1259\mu\text{M}\cdot\text{hr}/\text{MAC}\cdot\text{hr}$ ). Fluoride half-life was also significantly prolonged in hepatically-impaired patients (mean  $t_{1/2\text{ monophasic}}$   $33\text{hrs}$ , range  $21\text{-}47\text{hrs}$ ); this may be a result of effects of hepatic impairment on renal elimination of fluoride. It has been suggested that hepatic insufficiency may lead to intra-renal vasoconstriction, stimulation of the renin-angiotensin system and reduced renal blood flow.<sup>48</sup> The obese patient study group had a higher mean fluoride  $C_{\text{max}}$  ( $38.0\mu\text{M}$ ) compared with non-obese patients ( $29.0\mu\text{M}$ ) but the overall ranges were comparable for the two groups (obese,  $23.1\text{-}77.5\mu\text{M}$ ; non-obese,  $8.7\text{-}62.0\mu\text{M}$ ).

In vitro evidence suggests that sevoflurane is primarily metabolized by cytochrome P450 (CYP) 2E1.<sup>28</sup> Unlike other isoforms, CYP 2E1 is not present in the human kidney,<sup>49,50</sup> and is not inducible by barbiturates and phenytoin.<sup>51,52</sup> The effect of phenobarbital on fluoride pharmacokinetics following sevoflurane administration was assessed in healthy subjects in Study SEVO-92-014.<sup>23</sup> The effect of disulfiram ( $1 \times 500\text{mg}$ ), a selective inhibitor of P450 2E1 activity, on fluoride and HFIP pharmacokinetics following sevoflurane administration, was assessed in adult patients in Study SEVO-93-037.<sup>24</sup> Administration of phenobarbital did not alter fluoride pharmacokinetics following administration of sevoflurane. No significant differences

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<sup>23</sup> "range" - represents range of mean values

were observed with respect to  $T_{max}$ ,  $t_{1/2}$ , elimination rate constant, area under the curve, cumulative amount excreted or renal clearance for inorganic fluoride between subjects administered placebo or those administered phenobarbital for 2 weeks prior to sevoflurane exposure. Administration of disulfiram significantly inhibited the production of fluoride and HFIP following sevoflurane administration. This confirms the hypothesis that sevoflurane appears to be primarily metabolized by cytochrome P450 (CYP) 2E1.

Maternal and neonatal serum fluoride determinations following sevoflurane administration (mean of 0.42 MAC-hr for 0.9 hrs) were obtained in patients undergoing cesarean section. Maternal blood samples were obtained preoperatively and 24 hours post anesthesia. Arterial umbilical samples were collected at birth. At approximately 24 hours post-anesthesia, the mean maternal serum fluoride concentration was  $3.5\mu\text{M}$  (range:  $1.7\text{-}7.7\mu\text{M}$ ). The mean duration of neonatal exposure to sevoflurane was 9 minutes, with a maximum duration of 20 minutes. The mean fluoride concentration in the neonate at birth was  $2.3\mu\text{M}$  (range:  $0.9\text{-}6.3\mu\text{M}$ ).

Compound A concentrations were measured in one pharmacokinetic study (522). Sevoflurane was administered via a low flow circle absorption delivery system. Flow rate, temperature of the  $\text{CO}_2$  absorbent canister and dose were not indicated in the study report. Sodalime was the absorbent used for twelve subjects and baralyme was used for eight subjects. The mean maximum inspired and expired concentrations were approximately 17ppm (CV=121%, range 2-61ppm) and 11 ppm (CV=113%, range 2-38ppm) respectively for the baralyme group. The mean maximum inspired and expired concentrations were approximately 7ppm (CV=80%, range 3-15ppm) and 4 ppm (CV=70%, range 1-7ppm) respectively for the sodalime group. Other investigators (Bito and Ikeda have reported concentrations of 19.5 ppm (range 12.0-30.0ppm) with sodalime and 27.9 (range 18.3-37.8 ppm) with baralyme at a fresh gas flow rate of 1L/min. It is of concern that the sponsor has elected to pay minimal heed to the kinetics of this product in the pharmacokinetic section of the submission, particularly since it has been reported to have toxic properties in rats. Further details will be requested from the sponsor concerning Compound A concentrations as a function of flow rate and dose of sevoflurane administered.

#### 4 RECOMMENDATIONS

In conclusion, the sponsor has provided evidence of adequate investigations of the pharmacokinetics of this new volatile agent and thus the product is approvable according to the requirements of the Division of Biopharmaceutics.

As the sponsor has committed to completing a clinical study of low-flow general anesthesia with sevoflurane in renally impaired patients during a recent Anesthetic and Life support Drug Advisory Committee meeting (Jan 17 - Jan. 18, 1995), the sponsor is encouraged to design a protocol that would permit the validation of a physiological model. The availability of such a model would enhance the understanding of the disposition of this agent particularly in special populations (eg obese population, pediatric population) or in those populations which manifest a particular disease state (particular respiratory diseases). The sponsor is encouraged to develop

the protocol in conjunction with pharmacokinetic representatives at the FDA.

**5 SIGN-OFF**

Reviewed by:

*P. A. Lockwood 26 February 1995 (original signing date)*

Peter Lockwood, MS                      December 13, 1994 (1st draft)  
Pharmacokineticist                      March 6, 1995; 1994 (final )

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*Ruth E. Stevens 3-3-95 (original sign d/date)*

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## 7 PHARMACOKINETICS

### 7.1 Pharmacokinetic parameters of sevoflurane; (non-compartmental analysis)

In the three studies in which sevoflurane blood concentrations were measured, adult patients were exposed to sevoflurane at concentrations and durations appropriate to their surgical needs. Blood concentrations were obtained during and following anesthesia in studies SEVO-93-037 and 520 and preoperatively and following anesthesia in study 522. The standard compartmental analysis parameter estimates are displayed below and in some instances reflect exposure to sevoflurane in the particular studies rather than being characteristic of the drug.  $C_{max}$  estimates determined from 520 and SEVO-93-037 are comparable. This is to be expected given the similar MAC for both studies. The lower  $C_{max}$  determined in study 522 is attributable to administration of sevoflurane in a 1:1 nitrous oxide/oxygen mixture.

Table I Comparison of non-compartmental parameter estimates determined after administration of sevoflurane

Study	SEVO-93-037 (n=22)			520 (n=50)			522 (n=20)		
	Mean	CV	Range	Mean	CV	Range	Mean	CV	Range
MAC	1.29	4 %	1.16-1.39	1.27	21 %	0.72-2.13	0.44	30%	0.23 - 0.76
Duration (hr)	2.9	9 %	2.25-3.1	2.06	47 %	1-5.8	4.32	40%	2.1 - 8.7
Dose (Mac-hr)	3.71	10 %	3-4.2	2.6	51 %	1.14-7.47	1.9	55%	0.37 - 0.56
AUC <sub>0-t</sub> (µM.hr)	2672	26 %	1149-4077	1370	-	-	nd	-	-
AUCinf (µM.hr)	2676	26 %	1151-4080	nd	-	-	nd	-	-
C <sub>max</sub> (µM)	761	25 %	384-1148	716	35 %	345-1614	178	40%	105 - 314
t <sub>1/2</sub> (hr)	3.17	81 %	0.94-13.7	0.84	nd		0.81	36%	0.57 - 1.67

nd not determined

The volume of distribution at steady state ( $V_{ss}$ ) was determined according to the relationship  $V_{ss} = Clearance (Cl) * Mean Residence Time (MRT)$ .

The MRT was approximated as,  $MRT = AUMC / AUC - duration\ of\ anesthetic\ administration / 2$ .

Apparent Cl was computed as the sevoflurane dose / sevoflurane  $AUC_{0-t}$

These parameter estimates are displayed in Table 2 However, it must be borne in mind that these estimates are approximations only and that assumptions inherent within their calculation are violated. For example, the administration of sevoflurane was not a constant rate infusion and the

use of statistical moment theory to calculate  $V_{ss}$  in this regard implies a constant rate infusion. It is unclear as to what extent the violation of this assumption affects the size of the difference between the true and estimated parameter values.

Table 2 Parameter estimates from statistical moment theory for sevoflurane (SEVO-93-037).

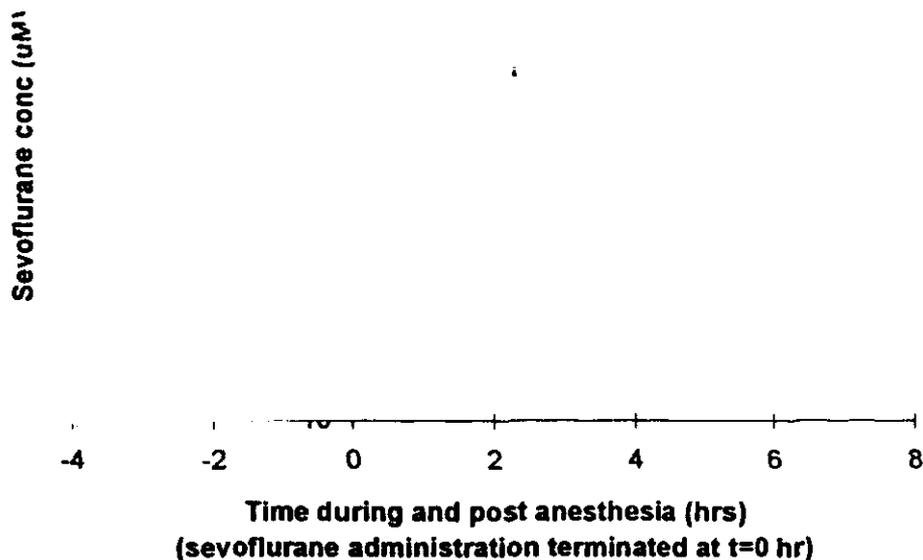
Parameter (n=22)	mean	cv	range
MRT (min)	80	22 %	50-126
AUC <sub>0-8hr</sub> (μM.hr)	2677	26 %	1151-4080
AUMC <sub>0-8hr</sub> (μM.hr)	441255	26 %	223278-625003
$V_{ss}$ (liters)	51.6	59 %	23-133
CL l/min	0.61	38 %	0.31-1.1

## 7.2 Disposition and disposition curves

The sponsor argues that sevoflurane exhibits biphasic blood concentration versus time disposition based on the results obtained in 520. This appears to be an oversimplification due to the fact that the sampling did not capture the true elimination phase and the duration of administration was too short. For example, in study 520, 8 samples were collected over the first 2 hours, 1 sample at 3 hours and the following sample at 8 hours. The duration of administration was approximately 2 hours and in virtually every instance no sevoflurane concentrations were detected at 8 hours. What the sample collection appears to have captured is the distribution and rapid clearance from two compartments, probably the vessel rich and muscle compartment.

In contrast, the sampling frequency in SEVO-93-037 was at 0, 1, 2, 3, 4, 5, & 7 hours after anesthesia and the average duration was approximately 3 hours. The average MAC was similar for the 2 studies. Inspection of individual and mean (see Figure 1) concentration-time profiles from SEVO-93-037, clearly suggest that the disposition and elimination of sevoflurane may be more adequately described by a triple exponential function rather than a biexponential function.

**Figure 1** Mean (—) and individual (---) concentration-time curves after admin. of sevoflurane (1.3 MAC for approx 3 hrs). Clearance from 3 compartments is indicated.



### 7.3 Compartmental parameter estimates

In Study GHBA-520, a second analysis based on a nonlinear mixed effects modeling approach was performed in order to better characterize the pharmacokinetic parameters of sevoflurane. A linear systems approach was used to derive the model equations, i.e a unit impulse response function was convolved with the input function. Ideally the result of this convolution gives an equation suitable for approximating sevoflurane blood concentrations. However, the input function used by the sponsor was not a true reflection of the surgical setting and the disposition function was oversimplified. Therefore the convolution is a poor representation of the system being characterized. This was emphasized when the individual fits following the post-hoc analysis were viewed. In almost every instance the model failed to fit peak concentrations. Additionally the variance associated with the typical value parameter estimates was high (approximately 50%) and the sponsor did not conduct any covariate analysis. Inspection of the relative standard error of the estimates ( $SE \cdot 100 / \text{Parm. estimate}$ ) in conjunction with the observed versus prediction scatter-plot, indicated that the model was not biased, but was imprecise. Furthermore there is no account of the predictability of this model. Thus, in conclusion, the outcome of this analysis is questionable. Population parameter estimates derived from the typical value estimates are summarized in Table 3.

**Table 3** Sevoflurane pharmacokinetic parameters from study 520. Non-compartmental and model estimates.

sevoflurane dosing parameter	Non-compartmental		Compartmental
	mean	cv	
duration (hr)	2.06	47%	
dose (MAC-hr)	2.6	47%	
AUC <sub>0-t</sub> (μM.hr)	1370	64%	1131
C <sub>max</sub> (μM)	716	35%	511
AUC <sub>0-t</sub> /dose (μM.hr/MAC-hr)	526	47%	435
t <sub>1/2</sub> (hr)	0.84	%	0.97

#### 7.4 Elimination and Half-life

Due to the different sampling schedules and durations of sevoflurane administration, the sponsor reported different values for the terminal half-life in the different studies. As has already been alluded to, sampling schedules and duration of anesthesia, will affect the half-life estimate. Assuming disposition may be more adequately described by a tri-exponential function, data from SEVO-93-037 suggests the terminal half life is more likely to approximate 3 hours (80% CV).

In study SEVO-93-037, estimates of sevoflurane dose were made from inspiratory and expiratory sevoflurane vapor concentrations and minute ventilation. Dose estimates (approximated in moles from pulmonary uptake computation used by Yasude et al.,<sup>27</sup>), in conjunction with quantities of fluoride and conjugated HFIP collected in the urine (approximated in moles), permitted estimation of the percent of the total sevoflurane dose eliminated as metabolite. Approximately 3.7% of the sevoflurane dose appeared in the urine as inorganic fluoride.

Prior work on sevoflurane (SEVO-92-014) indicates that up to 50% of fluoride clearance is nonrenal (via fluoride being taken up into bone). The results from SEVO-93-037 in conjunction with the results from SEVO-92-014, suggests that approximately 7.0% of the sevoflurane dose may be converted to fluoride. This is probably an over-estimate however, due to the fact that the uptake of fluoride into bone decreases with age and the mean age of patients in study SEVO-93-037 was almost twice that of those patients in SEVO-92-014.

The determination of the extent of the sevoflurane dose which may be converted to fluoride can be affected by diurnal variation, gastric pH, intestinal and urinary pH, food, the quantity of fluoride in the diet and fluoride toothpaste. Thus this should be kept in mind when considering

the above estimate. The total quantity of fluoride produced by metabolism of sevoflurane is further complicated in SEVO-93-037 because pre-dose baseline urinary fluorides were not obtained. Baseline concentrations from endogenous sources were estimated from background serum concentrations. Irrespective of the potential discrepancies, these results demonstrate that under steady state conditions, greater than 93% of sevoflurane dose inhaled is excreted via the lungs.

### 7.5 Dose Proportionality

Dose proportionality was assessed by examining the regression of dose-normalized AUC (AUC/dose) versus dose for male, female and all patients receiving sevoflurane in Study 520. However, given that the dose administered to each individual is determined by the effect and is therefore variable amongst individuals and that the physiological factors affecting the AUC will be variable amongst the individuals, it becomes difficult to draw clear conclusions regarding dose proportionality. The inferences derived from the correlation of two dependent variables are far less robust than the correlation derived from a dependent (dose) and independent variable (AUC). It is not surprising then, that a large degree of variability was observed when AUC/dose normalized to body weight was correlated with dose for all individuals in the study (see Figure 6). To have a clear understanding of dose proportionality in a true pharmacokinetic sense, subjects should be administered the same dose in a cross-over design study.

Bearing the above in mind, any inference from these results should be regarded with caution. Dose was approximated as MAC-Hr. The correlation coefficient of the regression was 0.0062 for females suggesting that the slope of the regression was not significantly different from zero (see Figure 1). The correlation coefficient of the same regression for males was 0.37 (see ?). A regression of AUC/dose normalized to body weight versus dose was conducted for males ( $R^2 = .0004$ ) and females ( $R^2 = 0.0004$ ) (see Figures 2-5).

Figure 2 AUC normalized to dose versus dose in females.

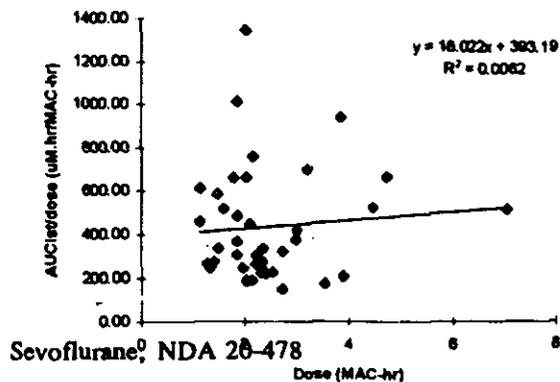
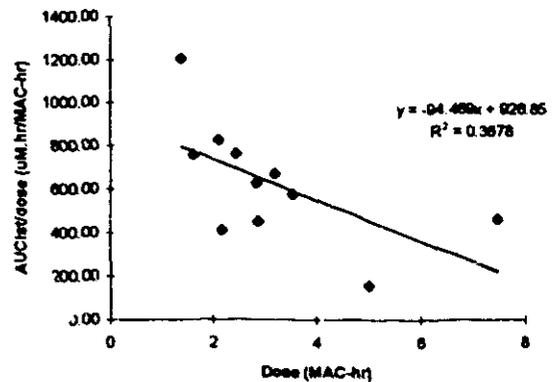
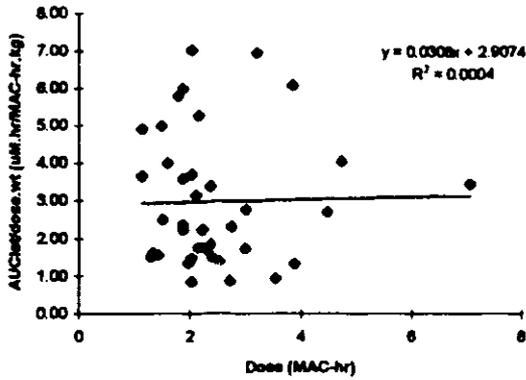


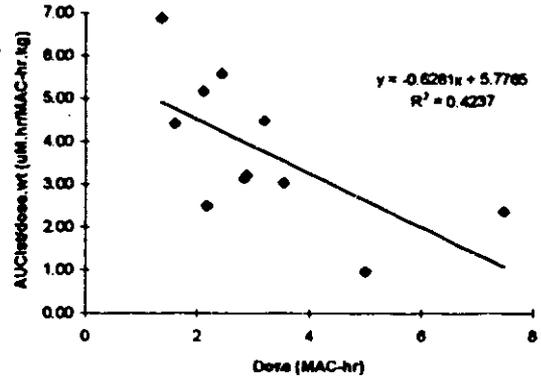
Figure 3 AUC<sub>0-1</sub> normalized to dose vs dose in males.



**Figure 4**  $AUC_{0-\infty}$ , normalized to dose and weight vs dose in females.

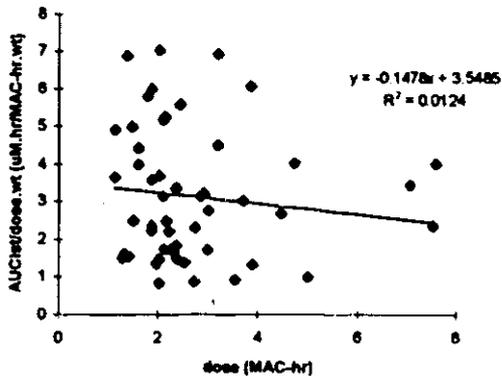


**Figure 5**  $AUC_{0-\infty}$ , normalized to dose and weight vs dose in males.



The sponsor evaluated dose proportionality in the absence of a gender covariate and determined that there was no relationship between  $AUC/dose$  and dose (see Figure 6). In any event the relationship between dose and inverse clearance requires a more controlled clinical study.

**Figure 6**  $AUC_{0-\infty}$ , normalised to dose vs dose in males and females (-520).



the above estimate. The total quantity of fluoride produced by metabolism of sevoflurane is further complicated in SEVO-93-037 because pre-dose baseline urinary fluorides were not obtained. Baseline concentrations from endogenous sources were estimated from background serum concentrations. Irrespective of the potential discrepancies, these results demonstrate that under steady state conditions, greater than 93% of sevoflurane dose inhaled is excreted via the lungs.

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Figure 2 AUC normalized to dose versus dose in females.

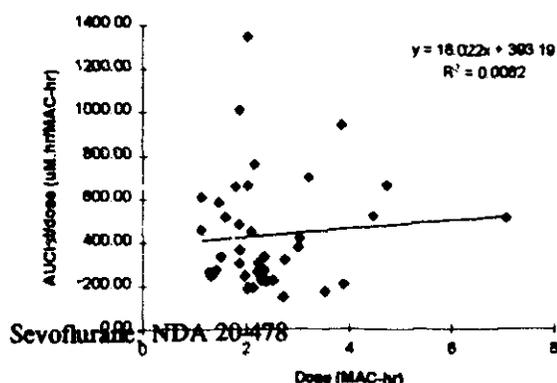
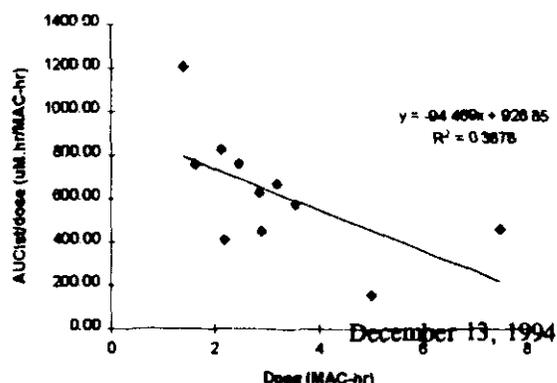
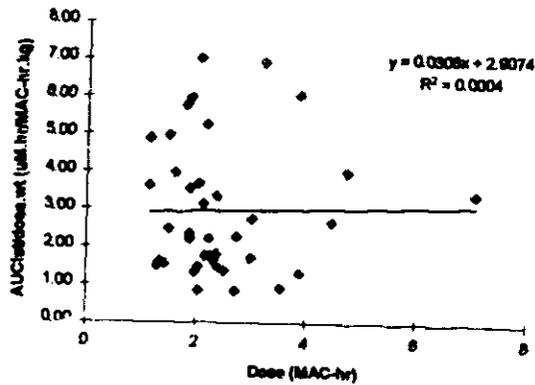


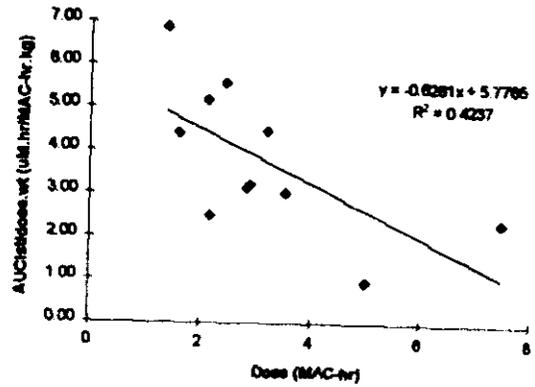
Figure 3 AUC<sub>0-1</sub> normalized to dose vs dose in males.



**Figure 4**  $AUC_{0-\infty}$  normalized to dose and weight vs dose in females.

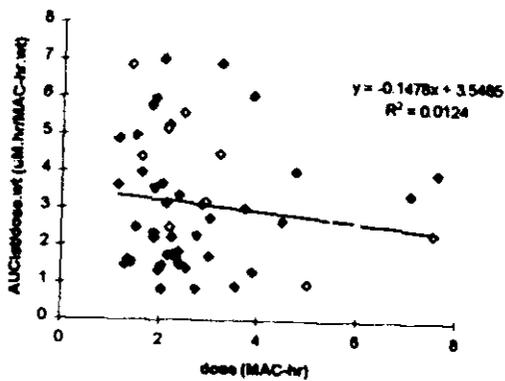


**Figure 5**  $AUC_{0-\infty}$  normalized to dose and weight vs dose in males.



The sponsor evaluated dose proportionality in the absence of a gender covariate and determined that there was no relationship between  $AUC/dose$  and dose (see Figure 6). In any event the relationship between dose and inverse clearance requires a more controlled clinical study.

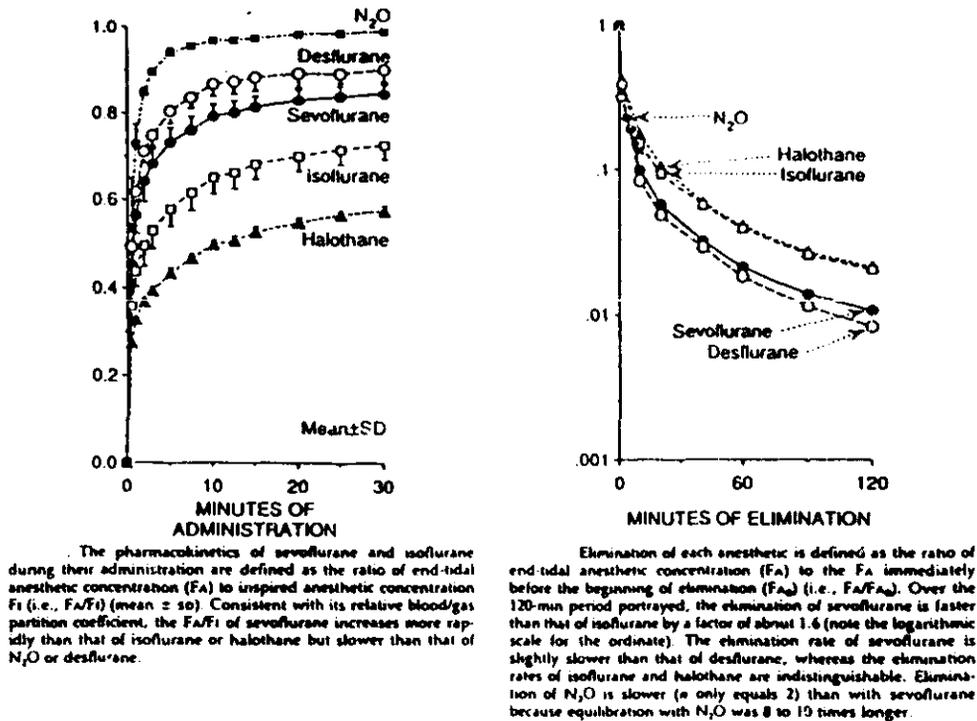
**Figure 6**  $AUC_{0-\infty}$  normalized to dose vs dose in males and females (520).



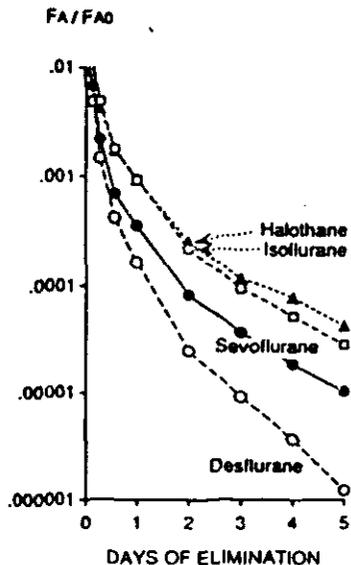
### 7.5.1 Washin-Washout Characteristics

The kinetics of sevoflurane (1.0% in 65% N<sub>2</sub>O & 35% O<sub>2</sub>) and isoflurane (0.6% in 65% N<sub>2</sub>O & 35% O<sub>2</sub>) with respect to equilibration with and elimination from tissue, were compared to that of nitrous oxide in seven healthy male subjects. The rate at which the alveolar (end-tidal) concentration (Fa) of nitrous oxide increased toward an inspired concentration (Fi) of 65-70% was measured. Sevoflurane or isoflurane was administered after administering nitrous oxide for 30 minutes. The concurrent rise in Fa and mixed expired concentrations (Fm) for these gases were then measured for 30 minutes. The ratio of Fa/Fi was used to define the pharmacokinetics during anesthetic administration. The ratio of Fa/Fa<sub>0</sub> was used to define anesthetic elimination, where Fa<sub>0</sub> is the alveolar concentration of anesthetic found immediately before discontinuing administration of sevoflurane and isoflurane. The Fa/Fi and Fa/Fa<sub>0</sub> variables determined in this study were compared with those determined for desflurane and halothane in a parallel study. The outcome of the above-mentioned comparisons have been previously published but were not included in this NDA. Mean (± SD) Fa/Fi values during the 30 minutes of administration, Fa/Fa<sub>0</sub> values for up to 5 days after discontinuing anesthesia are indicated in Figures 7 & 8.

Figure 7 Washin and washout kinetics of sevoflurane compared with other volatile anesthetics.



**Figure 8** Elimination of sevoflurane over 5 days compared with other volatile anesthetics.



The terminal elimination of sevoflurane is faster than that of isoflurane but is slower than that of desflurane. After 2-5 days, there is a two- to threefold difference between the values for sevoflurane and isoflurane. The difference between the values for desflurane and sevoflurane progressively increase after day 1 and approach eightfold by day 5.

## 7.6 Compartmental analysis

For each subject, a five-compartment mammillary model was fit simultaneously to the concentration of sevoflurane in end-tidal gas ( $F_a$ ) and the rate of excretion of the anesthetic via the lungs by using five differential equations to describe the rate of change in anesthetic concentration in each compartment. The same was also done for isoflurane. The five compartments were interpreted as representing the lungs, vessel-rich group, muscle group, a layer of fat that receives anesthetic from adjacent vessel-rich organs by intertissue diffusion (fourth compartment), and fat group. From the mammillary rate constants, time constants were calculated. Time constants reflect the time a molecule of gas would spend in a compartment, given that there is no input. (The use of time constants (reciprocal of the rate constant) is derived from tracer kinetics). Sevoflurane mammillary time constants were smaller than those for isoflurane for the lungs but did not differ for the other compartments. Constants are displayed below. Perusal of the ratio of rate constants indicates the sink capacities of the 4th and 5th compartments; i.e. for the 5th compartment, the amount of time that drug is time required to leave is 64 times greater than the amount of time required to enter. These constants were determined from the washout data only and the reason for this is unclear. It would have been more appropriate to model both the washin and washout data simultaneously. This may have reduced the variability obtained in the parameter estimates and provided a more robust model. Validation of the model is yet to be described.

**Table 4** Rate constants determined from compartmental analysis of sevoflurane washout data. (Yasuda et al., 1991<sup>27</sup>).

rate constant	mean	cv	ratio	
k10	1.78	18%	k12/k21	4
k20	0.0094	182%	k13/k31	10
k12	0.709	20%	k14/k441	40
k13	0.223	16%	k15/k51	64
k14	0.125	45%		
k15	0.032	63%		
k21	0.194	47%		
k31	0.0231	89%		
k41	0.00313	60%		
k51	0.0005	24%		

### 7.7 Protein Binding

Although not clinically relevant, sevoflurane exhibited saturable, fatty acid-displaceable binding to bovine serum albumin ( $K_d=4.5$  mmole/L). Comparable *in vitro* results were obtained with halothane ( $K_d=1.3$  mmole/L) and methoxyflurane ( $K_d=2.6$  mmole/L). This suggests that the fatty acid binding domains are probable sites of volatile anesthetic interaction with albumin. Sevoflurane, halothane and methoxyflurane were found to displace isoflurane from albumin fatty acid binding sites. The inhibitory binding constants ( $K_i$ ) closely resembled the dissociation constants. This data indicates that volatile anesthetics can bind at similar sites on a protein but have different affinities. Furthermore this might be considered as evidence for volatile anesthetics acting by binding to a target protein site in contrast to the traditional view of their being 'non specific drugs' that act by perturbing the structure of lipid membranes. Differences in potency might therefore be attributable in part to differences in affinity for a target protein.

The binding constants are 3-10 times the concentrations required to produce anesthesia in animals. This is not surprising since albumin is not a target protein responsible for producing

anesthesia. The binding to fatty acid sites on albumin may yield clues as to the actual target sites.

### 7.7.1 Interaction of sevoflurane with albumin binding drugs.

No studies have been conducted which specifically investigate the influence of sevoflurane on the binding to human serum albumin (HSA) of highly bound drugs. Studies have been conducted with other fluorinated volatile anesthetics however and an elevation of the free fraction of highly bound drugs has been demonstrated in the presence of these compounds. Since it has been demonstrated that sevoflurane displaces isoflurane from albumin and that there may be a common albumin binding site for fluorinated anesthetics, then binding studies using other fluorinated agents may be characteristic of sevoflurane activity. Thus the influence of isoflurane, halothane and enflurane on the in vitro binding of diazepam, phenytoin and warfarin (2.25  $\mu\text{M/L}$ , 85 $\mu\text{M/L}$  & 10 $\mu\text{M/L}$ ) to albumin are reported below.

The influence of the anesthetics on drug binding was determined by placing dialysis cells in a gas-tight glass desiccator into which anesthetic was delivered by a vaporizer. Isoflurane under clinically relevant conditions (1 MAC (1.1%), 37 degree C) increased the free fractions of diazepam and phenytoin by 16% and 11% respectively. Isoflurane did not interact with warfarin binding. Enflurane (1 MAC (1.7%), 37 degree C) increased the free fraction of diazepam by approximately 60%. No effect was apparent for halothane (1 MAC (0.8%), 37 degree C) The difference between enflurane and isoflurane may be a consequence of the higher MAC value. Enflurane (5%) decreased the serum binding of propranolol and prazosin by 40% & 25% respectively.

Therefore, based on the displacing properties of other fluorinated volatile anesthetics, there is evidence to suggest that sevoflurane will displace drug from serum bound proteins. Whether this has an impact will be determined by the change in free drug concentration which is in turn governed by the extent of redistribution and the intrinsic clearance of the displaced drug ( $CL_{int} = CL_{int} \cdot f_{ub}$ ). The consequences of drug displacement will be complicated by the simultaneous displacement of drug from tissue proteins since volatile anesthetics penetrate all biological barriers. This may counteract any redistribution that takes place following displacement from serum proteins and increase the likelihood of side effects. (Drugs 25, 495; McElnay and Darcey). Alternatively, clinical concentrations of the anesthetic may affect (decrease or inhibit) metabolism. (Acta, Pharmacol & Toxicol., Aune et al., 1983, 53, 363; Acute effects of halothane and enflurane on drug metabolism) and thus have clinical significance in the first few hours following anesthesia.

In conclusion, based on the evidence of other fluorinated volatile anesthetics, it would appear that sevoflurane may displace drugs from serum and tissue proteins causing increased free drug concentration. The relevance of this to clinical anesthesia remains to be settled and should be determined.

## 7.8 Metabolism and metabolites

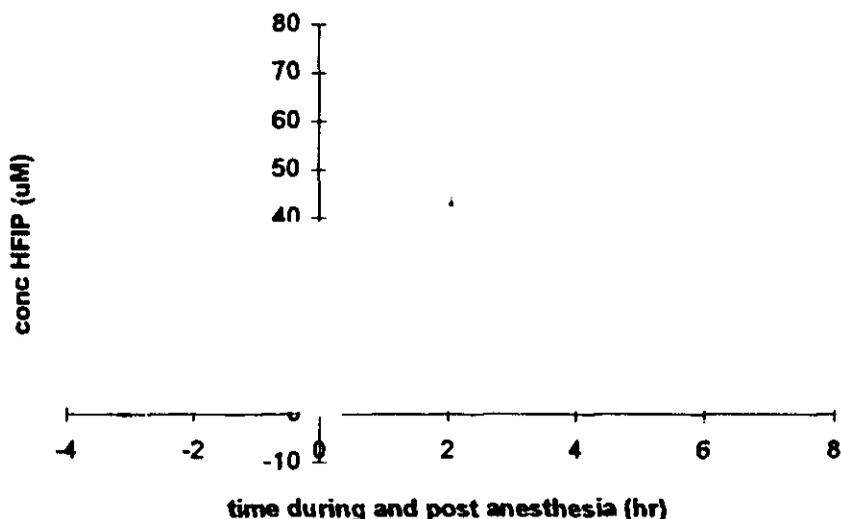
### 7.8.1 Pharmacokinetics of HFIP

Previously published studies have demonstrated that sevoflurane is metabolized to hexafluoroisopropanol (HFIP) in man with release of inorganic fluoride.<sup>29-32</sup> The characterization of inorganic fluoride levels in blood during and after administration of sevoflurane is the subject of the following section. Blood HFIP concentrations were determined in two studies: (SEVO-93-037 & 522) of adult patients undergoing elective surgical procedures.<sup>2, 24</sup> In study SEVO-93-037 free plus conjugated HFIP were measured in blood and urine. Free HFIP concentrations were negligible (generally below the limit of quantitation, 5  $\mu\text{M}$ ), and therefore the results reflect bound HFIP. Individual and mean concentration-time plots are displayed in Figure 9 and indicate a wide range of intersubject variability. The maximum concentration observed in one subject was 71.6  $\mu\text{M}$  at 2 hours post anesthesia. Two other subjects exhibited maximum concentrations of approximately 60 $\mu\text{M}$  at 2 and 4 hours post anesthesia. It is difficult to determine whether these measurements are true or artifactual because of the deficiency of measurements in the vicinity of  $C_{\text{max}}$ . What is clear however is the long half life of this compound.

In Study 522, free (not conjugated) plasma HFIP concentrations were detectable in 4 of 20 patients at only two or three sampling times. (The sampling schedule for 522 was at 0, 1, 2, 4, 6, 8, 12, & 24 hours after termination of anesthetic administration). The maximum observed HFIP concentration was 66 $\mu\text{M}$ , occurring 4 hours after termination of sevoflurane administration in one patient.

In control patients of Study Sevo-93-037, urinary excretion data collected over 96 hours was used to calculate the harmonic mean. Excretion rate (log scale) versus time was plotted for each individual and the data points fitted by linear regression. Individual half-lives were

**Figure 9** Individual and mean concentration-time curves for HFIP during and after administration of sevoflurane (mean MAC = 1.27(CV=5%), mean duration = 2.9hr (CV=9%))



determined from the slope of each fit and meaned to obtain an average  $t_{1/2}$  of 19.1 (CV=43%) hours. Collection intervals were of 12 hours duration.

The area under the conjugated HFIP concentration versus time curve from the start of anesthetic administration through the end of blood sampling,  $AUC_{0-11}$  hr was determined by the linear trapezoidal rule. This, in conjunction with the amount of conjugated HFIP collected in the first urine collection of 0-12 hours was used to approximate the renal clearance for each individual. The mean renal clearance for HFIP was 284 mL/min (CV=39%). Since the magnitude of the renal clearance exceeds normal glomerular filtration rates (120mls plasma water/min.), it is inferred that this metabolite is both filtered and actively secreted. Approximately 4.9% of the sevoflurane dose was collected in the urine as HFIP (free plus conjugated).

### 7.8.2 Pharmacokinetics of Inorganic Fluoride Metabolite

Inorganic fluoride concentrations in blood following sevoflurane administration were characterized in 24 studies.<sup>1-24</sup> These include two studies in healthy subjects, eight studies in adult patients undergoing elective surgical procedures, one study in patients involving multiple exposures to sevoflurane, six studies in pediatric patients, one study in elderly patients, two studies in patients with renal impairment, one study in patients with hepatic impairment, and one study in patients undergoing elective cesarean section. Two additional studies addressed drug interactions with sevoflurane including one study in healthy subjects examining the effect of phenobarbital on serum fluoride concentrations following sevoflurane administration, and one study in patients examining the effect of disulfiram on sevoflurane defluorination.

### 7.8.2.1 Inorganic fluoride non-compartmental pharmacokinetic results in studies of adult patients

Inorganic fluoride  $C_{max}$ ,  $T_{max}$ , and  $t_{1/2}$  following sevoflurane administration were determined in nine studies involving adult patients undergoing elective surgical procedures.<sup>1,2,5-10</sup> The estimates of these parameters are listed in Table 6.

As with sevoflurane, fluoride ion concentrations are influenced by the duration of anesthesia, the MAC administered and the composition of the anesthetic gas mixture. In studies 520, 523 and SEVO-93-037 anesthesia was maintained purely with sevoflurane for periods ranging from 1 to 6 hours. Peak fluoride concentrations for these studies ranged between  $12\mu\text{M}$  and  $90\mu\text{M}$ . Peak concentrations occurred within 2 hours of the end of anesthesia. Sphagetti plots of fluoride ion concentration versus time are displayed in Figures 10-13 for studies 520 ( $n=50$ ) and SEVO-93-037 ( $n=10$ ). (Plots were not examined for 523 due to the limited sampling). These plots demonstrate that fluoride ion concentrations do not exceed  $70\mu\text{M}$ . In most instances fluoride ion concentrations are below  $30\mu\text{M}$  after 5 hours (see Figure 11). The mean  $C_{max}$  for 520, SEVO-93-037 and 523 were  $33\mu\text{M}$ ,  $36\mu\text{M}$  and  $45\mu\text{M}$  respectively.

It would be anticipated that administration of sevoflurane at a lower MAC for longer durations would produce similar results to those previously discussed. Mean values for  $C_{max}$  were fairly consistent across the eight studies ranging from  $24.7\mu\text{M}$  to  $45.1\mu\text{M}$ . The maximum observed concentrations in each study ranged from  $48.4\mu\text{M}$  to  $110.7\mu\text{M}$ .

The sponsor argues that there is a correlation between  $T_{max}$  and the duration of sevoflurane administration; i.e. the time to peak fluoride concentration following termination of sevoflurane administration was shorter with a longer duration of administration<sup>6</sup>. The sponsor corroborates this observation with results from a simulation. The simulation does show that the time to peak fluoride concentration following termination of sevoflurane administration was shorter with longer duration of administration but there is a strong case for arguing that the model is inappropriate (bi/triphasic not monophasic disposition; 300% variability in precision and error of parameter estimates, 700% variability in residual error estimate).

With regard to the studies that the sponsor uses to support the supposition, they are all deficient in terms of either subject number or aberrant sample collection. Additionally, the difference in measured concentrations varied by less than the coefficient of variation for up to 2 hours after administration of the anesthetic was terminated in some subjects; (i.e. patient 1, 522,  $19.77\mu\text{M}$  at end of anesthesia,  $20.8\mu\text{M}$  at 1 hour and  $20.2\mu\text{M}$  at 2 hours; CV at this concentration  $\approx 5\%$ ). Variability in the assay will have a marked effect on the  $T_{max}$  estimate.

In conclusion, this relationship should be considered as speculative.

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<sup>6</sup> (i.e. Study GHBA-522 (4.3 hr,  $T_{max} = 0.75\text{hr}$ ) Study GHBA-528 (duration = 6.4hr,  $T_{max} = 0.25\text{ hr}$ ), and Study SEVO-93-035 (duration = 4.6 hr,  $T_{max} = 0.15\text{ h}$ )

### 7.8.2.2 Fluoride disposition curves and half-life

Inspection of individual fluoride ion concentration-time curves indicated monophasic and biphasic fluoride ion elimination. Generally about 70%-80% of the study population demonstrated monophasic pharmacokinetics. The sponsor reports that, based on eight studies the harmonic mean half-lives for this group ranged from 9 to 21 hours. It is the reviewers opinion that 15-22 hours is a more approximate estimate for the following reasons and that half-life estimates below 15 hours should be excluded. The half-life determined in Study GHBA-528 was the mean of only three subjects. The half-life determined in Study SEVO-92-003 was an overall half-life estimated by normalizing the data to  $C_{max}$  and the time of  $C_{max}$  was normalized to zero for all patients. The half-life was computed as  $\ln(2)/K$  where K is the negative slope obtained by linear regression of log-transformed normalized concentration time data for all patients. Study GHBA-528 included elderly, obese and patients undergoing cardiac surgery. Additionally all data was treated as a declining mono-exponentially when inspection indicated that the disposition of the fluoride ion for some individuals was more appropriately described in terms of biphasic disposition kinetics. Thus this data should be reanalyzed. Finally, the sampling schedule in study GHBA-528 may not have captured the true fluoride elimination phase. The longer half-lives observed in Studies SEVO-93-037 (21.4 hr), SEVO-92-003 (15.4 hr), SEVO-92-005 (14.7 hr), and SEVO-93-035 (12.0 hr) may be a result of being able to quantify fluoride at lower concentrations and being able to resolve two pharmacokinetic phases for a subset of patients in each of these studies.

The most reliable half-life estimate would be from the two studies with larger patient numbers; SEVO-92-003 and SEVO-92-005. Approximately 20-30% of the patients exhibited biphasic elimination. The mean  $\alpha$ -phase half-lives ranged from 1.4 to 2.7 hours and the mean  $\beta$ -phase half-lives ranged from 20.1 to 22.9 hours. These estimates of the  $\beta$ -phase half-lives are more consistent with the 15-22 hour range determined from the monophasic population.

Although multiphasic fluoride disposition has been reported previously,<sup>41,42</sup> caution in interpretation of these results should be exercised. The ability to detect multiphasic dispositional pharmacokinetics is dependent upon several factors including duration of drug administration, sampling scheme, and baseline fluoride concentrations. Baseline concentrations of fluoride may fluctuate as a function of fluorinated drinking water, circadian variation,<sup>43</sup> and meal-related changes in gastric fluoride absorption.<sup>44,45</sup> In the computation of half-life, pre-dose fluoride concentrations were taken as baseline values and were subtracted from fluoride concentrations obtained during and after anesthesia administration. Error in baseline estimates and/or fluctuation in baseline fluoride concentrations may make a log-linear disposition appear non-linear. Thus, some of the apparent multiphasic nature of the disposition curve may be artifactual. Nonetheless, the pharmacokinetic characterizations presented herein provide a reasonable description of the magnitude and duration of fluoride exposure following sevoflurane administration.

Fi  
fc 10 Individual fluoride ion concentrations during and  
ours post anesthesia; (520).

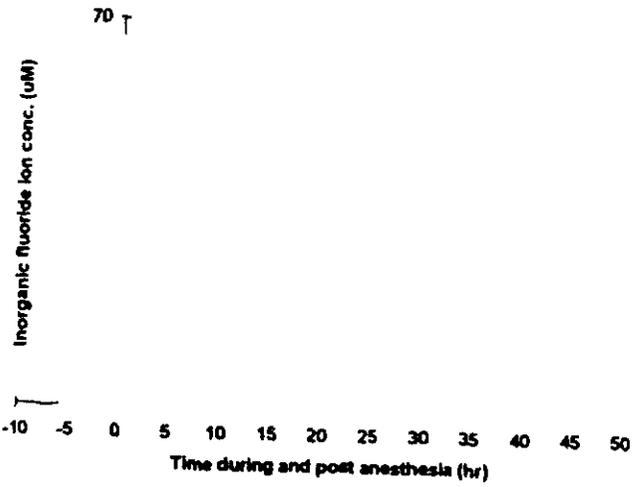
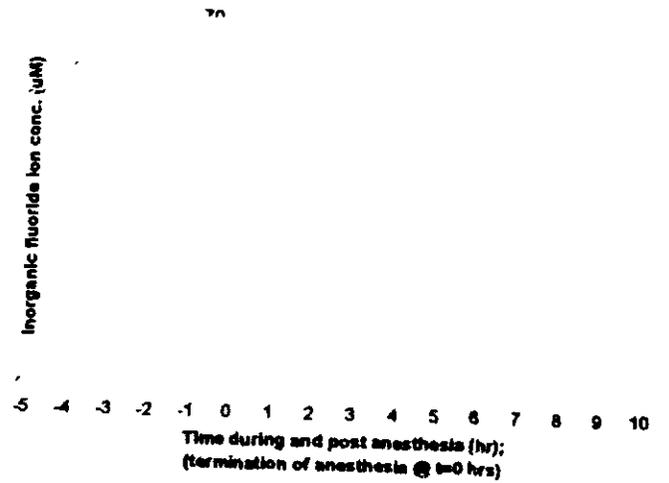


Figure 11 Individual fluoride ion concentrations  
during 1st 10 hours post anesthesia; (520).



Fi  
di 12 Individual fluoride ion concentrations  
and post anesthesia; (SEVO-93-037).

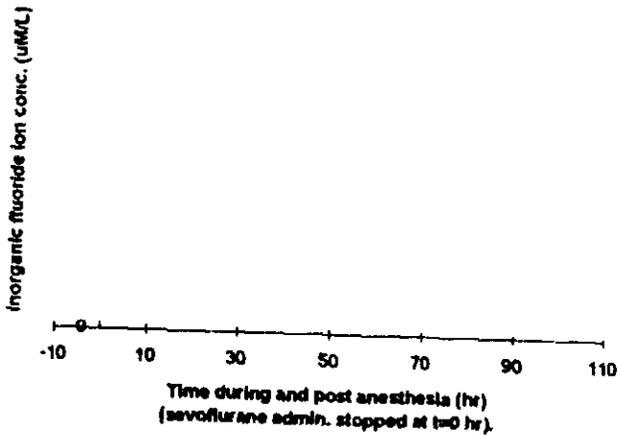


Figure 13 Individual fluoride ion concentrations (log  
scale) during and post anesthesia; (SEVO-93-037).

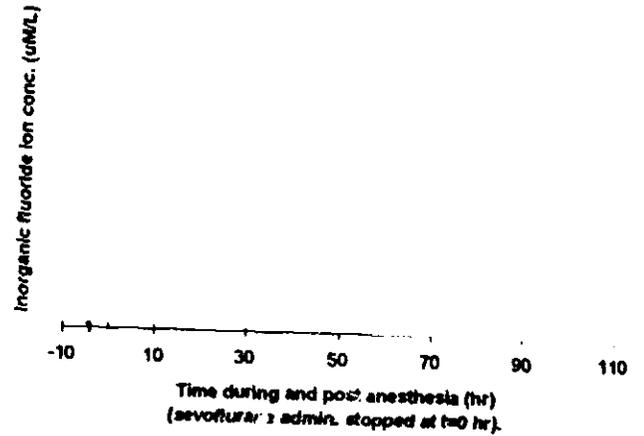


Table 5 Mean fluoride non-compartmental pharmacokinetic parameters in adult patient studies

Study	Units	SEVO-93-037	SEVO-92-003	SEVO-92-005	SEVO-93-035	-528	-520	-52
last sample time	(hr)	60	70	72	48	72	24 (n=43)	3
N		10	70	156	4	8	50	20
Duration (%CV)	(hr)	2.91	2.1 (51%) (0.8-5.9)	3.9 (43%)	4.6 (26%)	6.9 (41%)	2.06 (21%)	2.6 (16%)
MAC (%CV)		1.27 (5.2%)	0.5 (35%)	0.49	0.31	0.51 (41%)	1.3 (50%)	1
Dose (%CV)	MAC-hr	3.7 (11%)	1.1 (71%)	1.9 (60%)	1.4 (20%)	3.23 (75%)	2.6 (50%)	2.5 (20%)
C <sub>max</sub> (%CV)	μM	36 (34%)	25 (43%)	32 (39%)	34.6 (34%)	38.2 (31%)	33.1 (42%)	45 (37%)
Range		22-60	11-63	7-114	20-48	23-60	12-75	28-90
T <sub>max</sub>	hrs	2.01 (60%)	not determined	1.6 (227%)	0.15 (74%)	not determined	not determined	not determined
t <sub>1/2</sub> (hrs) (%CV)	monophasic	21.4 (95) <sup>†</sup>	15.4 (45%) <sup>†</sup> (5.3-36)	14.7 (54%)	12 (90%)	9.04 (36%)	11.4 <sup>††</sup>	11 (27%)
	n	10	43	116	4	3	50	20
	α - phase		2.7 (67%) (0.2-8.4)	2.7 (71%)	2.3 (65%)	2.0 (48%)	-	-
	β - phase		23.2 (40%)	22.7 (32%)	22.9 (6%)	20.4 (64%)	-	-
	n		20	35	4	5	-	-

harmonic mean and pseudo standard deviation; <sup>†</sup> half life estimated by linear regression of normalized post admin. data (see 520 txt)

### 7.8.2.3 Dose proportionality

In study SEVO-93-044 sevoflurane and enflurane were administered for induction and maintenance of anesthesia in healthy male subjects. During maintenance, a constant concentration of 1.3 MAC was administered in an O<sub>2</sub>/air mixture (minimum inspired oxygen concentration of 30%); duration of anesthesia was varied to produce exposure of 3, 6 or 9 MAC hours. In study -536, following intravenous induction sevoflurane was administered in 30-40% oxygen at a rate of 1.0-1.2 MAC for 2.5-3.0 hours (3.0 MAC-hr group) or 8.0-9.6 hours (9.6 MAC-hr group) to healthy male subjects. In both studies blood samples for determination of inorganic fluoride concentrations were collected prior to induction, during sevoflurane administration, and post-anesthesia. The pharmacokinetic parameter results are summarized in Table 5:

### 7.8.2.4 Extended and repeat exposure

Inorganic fluoride concentrations following extended exposure (approximately 1.07 MAC for 3 and 6 hours, and 1.14 MAC for 8 hours) to sevoflurane were compared to those following enflurane (1.05 MAC for 6 hours and 1 MAC for 9.15 hours) in healthy male subjects (Study SEVO-93-044). Following administration of up to 9 MAC-hr of sevoflurane, peak serum fluoride concentrations and half-life values were similar (not statistically significantly different) to those observed after administration of lower sevoflurane doses. Mean peak serum fluoride concentrations were similar for all three doses. A slightly higher mean C<sub>max</sub> was observed following exposure to 9 MAC hours of sevoflurane (approximately 37μM vs 31μM) and this could be accounted for by the higher MAC at this duration.

The effect of repeat exposure to sevoflurane on fluoride concentrations in blood was examined in patients undergoing multiple surgical procedures in Study -531. Increases in fluoride C<sub>max</sub> values with second and third exposures to sevoflurane within a 2-week period appeared to be due to the higher doses of sevoflurane (longer duration of anesthesia) administered during these surgeries (mean C<sub>max; exposure 1</sub> = 29.2μM, 57%CV, range 10-81μM; mean C<sub>max; exposure 2</sub> = 42.5μM, 57%CV, range 18-111μM; mean C<sub>max; exposure 3</sub> = 49.9μM, 56%CV, range 29-100μM). There were no significant differences in fluoride t<sub>1/2</sub> among the first, second and third exposures. Mean monophasic half-lives for the first, second and third exposure were 5.3hr (84%CV; range 1.5-14.7), 5.9hr (64%CV; range 1.9-14.7) and 10.2hr (37%CV; range 6.5-13.4) respectively.

However these results are misleading and are a consequence of a poor study design. The outcome of this study, is that it should only be considered to evaluate the safety of multiple doses of sevoflurane. The study fails to offer any insight into the accumulation of inorganic fluoride due to the absence of any control on the MAC and duration of anesthetic administered or gap times for sequential surgical procedures. For example, the second exposure for each individual was of different duration and generally higher MAC from the first, resulting in a larger dose (MAC-hr). Furthermore there were too few measurements to truly characterize the half-lives of the study participants such that it was not possible to differentiate whether possible accumulation was a consequence of the increased dose or residual fluoride concentrations.

Finally, there were too few subjects in the last group (third exposure, n=5) to consider the data meaningful.

**Table 6** Fluoride parameter estimates following varied exposures to sevoflurane (SEVO-93-044, 536).

Study		SEVO-93-044			536	
last sample time	(hr)	60	60	60	144	144
N		5	10	6	7	7
Duration (%CV)	(hr)	3.0 (6%)	5.8 (10%)	8.05 (3%)	2.8 (4%)	8.6 (4%)
MAC (%CV)		1.1 (5%)	1.1 (10%)	1.14 (3%)	1.06 (7%)	1.1(3%)
Dose (%CV)	MAC-hr	3.21 (3%)	6.2 (1%)	9.2 (1%)	3.0 (5%)	9.2 (1%)
C <sub>max</sub> (%CV)	μM	30.5 (26%)	32.1 (17%)	36.6 (12%)	25.4 (15%)	
Range		21-42	24-41	30-41	20-31	
t <sub>1/2</sub> (hrs) (%CV)	(monophase)	14 (26%)	18.5 (12%)	16.7 (17%)	not determined	not determined
	n	4	9	6		
	alpha phase	5	6.7			
	beta phase	20.3	18.6			
	n	1	1			
AUC <sub>0-1hr</sub> /Dose	(μM.hr/MAC-hr)	184 (35)	134 (23)	101 (14)	nd	nd
AUC <sub>0-144</sub> /Dose					186 (41%)	127 (27%)

## 7.8.2.5 Special Populations

### 7.8.2.5.1 Pediatric Populations

Inorganic fluoride concentrations following sevoflurane administration in pediatric patients were assessed in six studies: SEVO-92-001, SEVO-92-008, SEVO-92-015, -532, -533, and 534.<sup>13-18</sup> While recognizing that the definition for MAC in pediatric patients depends on age, the sponsor used the adult definition of MAC (2.05%) in all studies. Five of these studies included determinations of fluoride pharmacokinetic parameters as summarized below and displayed in Table 7.

In studies -532 and -533, patients received sevoflurane only. The MAC administered was similar in both studies and in males and females (approximately 1.4). The duration of anesthesia in study -533 was approximately twice as long as -532 (2 hours versus 1 hour). The mean fluoride  $C_{max}$  was very similar between studies (13-17 $\mu$ M) and within the studies for male and female subjects. The maximum concentration observed was 27 $\mu$ M in 1 male subject in study -532. There was no correlation between age or fluoride ion concentrations for males or females.  $T_{max}$  was approximately 35 minutes (50% CV) for males and females in study -532. This is likely to be the most reliable estimate of  $T_{max}$  as this was the only study in which a 30 minute sample was taken. Parameter estimates are displayed in Table 7 and scatter plots for -532, GHBA-533, SEVO-001 & SEVO-008 are displayed in Figures 15-17.

In studies SEVO-92-001, SEVO-92-008, and -533, sevoflurane was administered with nitrous oxide. The composition of sevoflurane/nitrous oxide administered to each individual or the concomitant administration of other drugs or anesthetics was not detailed in any of these studies. The sponsor does indicate that where sevoflurane was coadministered with nitrous oxide, up to 70% of the anesthetic gas mixture was nitrous oxide. What is intriguing with these studies is that administration of N<sub>2</sub>O with sevoflurane did not reduce the MAC.

The MAC (1.14-1.3) and duration (2-3 hours) were similar across studies and within male and females. The mean  $C_{max}$  for the fluoride ion ranged from approximately 14 to 21 $\mu$ M. A greater preponderance of subjects between the ages of 11 and 18 years were enrolled in these studies compared with -532 and -533. This was reflected in  $C_{max}$  concentrations approaching values observed in adult patients for some individuals. The maximum  $C_{max}$  observed in these studies was 45 $\mu$ M for a 10 year old female (SEVO-92-001).

In the remaining study, -534, plasma fluoride determinations were obtained only prior to and at one hour after anesthetic administration; the results for this study were similar to those previously obtained.

In Study SEVO-92-015, fluoride pharmacokinetics following multiple (2x) exposures to sevoflurane were assessed. There was no difference in the mean  $C_{max}$  following first and second exposure ( $C_{max}$  exposure 1 = 18.3 $\mu$ M,  $C_{max}$  exposure 2 = 20.0 $\mu$ M).

In conclusion, the half-life was observed to be lower in the pediatric population compared with adults. In this submission, mean half-lives in pediatric patients ranged from 1.8-9.7 hrs.

Parameter estimates in pediatric patients following administration of 1.27-1.44 MAC sevoflurane for 1 or 2 hours.

(sevoflurane only)		N	Age (Yrs)	Duration (%CV)  (hr)	MAC	Dose (%CV)  (MAC-hr)	C <sub>max</sub> (%CV)	T <sub>max</sub> (%CV)  (hr)	t <sub>1/2</sub> (%CV)  (hr)
532	males	61	0-11	0.8 (43%)	1.4 (10%)	1.1 (41%)	12.6 (33%)	0.6 (55%)	1.8 (57%) (n=61)
	females	16	1-8	0.9 (64%)	1.4 (9%)	1.3 (73%)	12.7 (36%)	0.6 (50%)	1.7 (41%) (n=14)
533	males	28	1-11	2.4 (50%)	1.3 (13%)	3.0 (48%)	16.7 (25%)		
	females	12	5-11	2.0 (68%)	1.4 (18%)	3.0 (83%)	14.3 (35%)		
(sevoflurane & nitrous oxide)									
SEVO-92-001	males	12	5-13	1.74 (45%)	1.31 (13%)	2.2 (46%)	21.4 (26%)		7.5 (96%) (n=10)
	females	13	5-13	2.1 (36%)	1.23 (13%)	2.6 (32%)	21.2 (41%)		9.7 (79%) (n=12)
SEVO-92-008	males	26	0-18	2.3 (51%)	1.14 (28%)	2.2 (57%)	18.4 (31%)		4.7 (80%) (n=25)
	females	16	3-18	2.4 (61%)	1.17 (27%)	2.3 (75%)	18.03 (40%)		7.8 (81%) (n=16)
533	males	24	1-11	2.2 (53%)	1.28 (18%)	2.8 (60%)	16.6 (26%)		
	females	16	3-9	1.8 (52%)	1.3 (20%)	2.3 (49%)	13.9 (33%)		
SEVO-92-015 Exposure 1			0-18	3.2 (69)	0.96	3.1 (47%)	18.3 (19%)	0.2 (365%)	1.54 (56%)
SEVO-92-015 Exposure 2			0-18	3.1 (73%)	0.93 (21%)	2.4 (46%)	20 (40%)	0.2 (260%)	0.97 (172%)

Figure 15 Scatter plot of max fluoride ion conc in pediatric females (SEV0-001 & 008, -532).

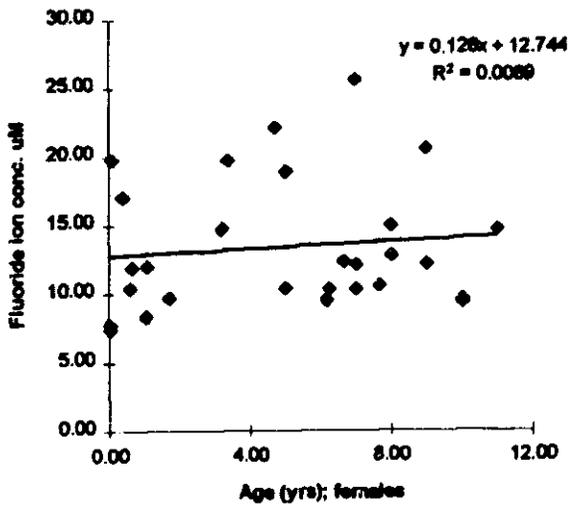


Figure 14 Scatter plot of maximum fluoride ion conc in pediatric males (SEV0-001,008 -532).

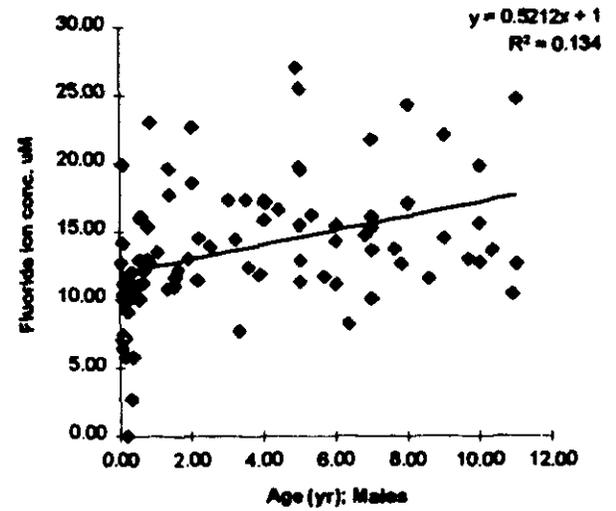


Figure 16 Scatter plot of max. fluoride ion conc in pediatric females (SEV0-001 & 008, -532).

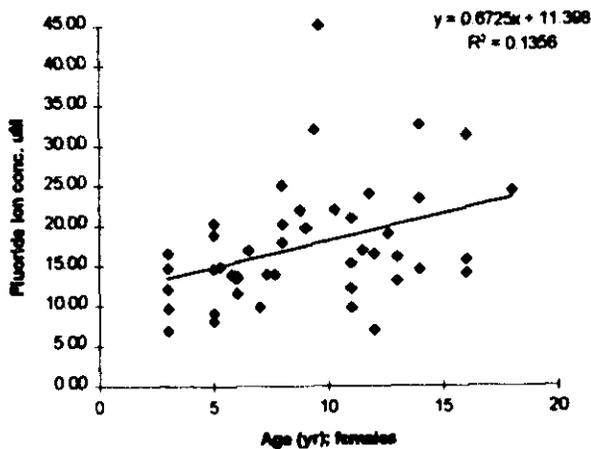
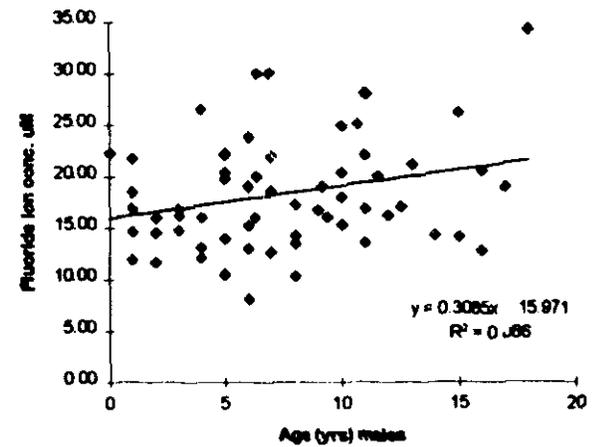


Figure 17 Scatter plot of max. fluoride ion conc in pediatric males (Study SEV0-001,008 -532).



### 7.8.2.5.2 Elderly Populations

Inorganic fluoride concentrations following sevoflurane administration to elderly patients were assessed in Study SEVO-92-012.<sup>19</sup> and -525. In SEVO-92-012 sevoflurane was administered with up to 70% nitrous oxide (30-50% oxygen) in patients > 65 years of age (ASA Class I, II and III) undergoing elective surgical procedures of up to 3 hours duration. Blood samples for determination of inorganic fluoride concentrations were collected pre-operatively, during sevoflurane administration, and post-anesthesia. The mean MAC administered to male and female patients was approximately 0.5 for a duration of approximately 2.5 hours. There was no difference in the fluorine  $C_{max}$  for elderly males (mean  $C_{max}$  = 24.12, 47%CV, range 7.5-45) or females (mean  $C_{max}$  = 28, 47%CV, range 11-50). A correlation was observed between maximum fluoride ion concentration for males and females although no correlation was observed between creatinine clearance per kg and fluoride ion concentration. These correlations are displayed in the following scatter plots. Peak fluoride concentrations were observed within two hours after termination of sevoflurane administration. Forty percent of male and female patients displayed biphasic disposition. Mean half-lives whether determined from a mono or biexponential disposition function were similar between elderly males and females and similar to values obtained in younger subjects in SEVO-92-003. Parameter estimates obtained in this study are displayed in Table 8.

Figure 18 Scatter plot of max. fluoride in conc in elderly females versus age (SEVO-92-012).

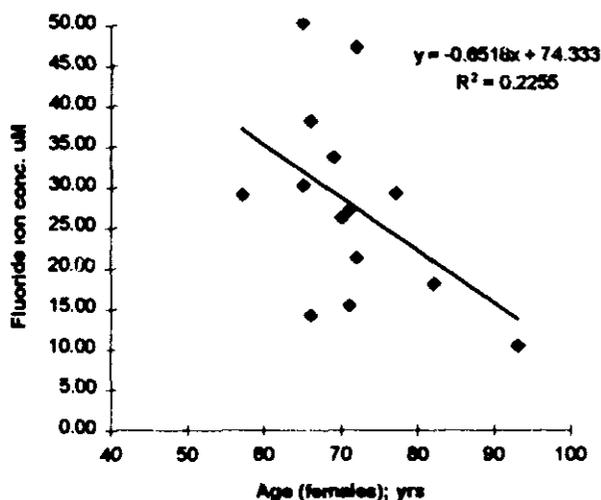
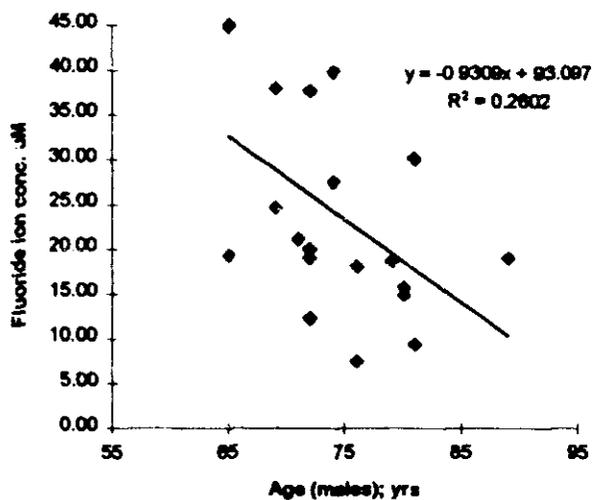


Figure 19 Scatter plot of fluoride in conc in elderly males versus age (SEVO-92-012).



**Table 8 Fluoride non-compartmental parameter estimates for elderly patients (SEVO-92-012).**

	units	females	range	CV	males	range	CV
n		14			20		
age (yr)		71.14	57-93	12%	74.1	65-89	8%
Sr Cr	$\mu\text{M/L}$	76.40	53-106	20%	86.63	35-123	25%
$\text{Cr}_d$	ml/min	65.00	42-113	30%	77.70	35-169	37%
$\text{Cr}_d/\text{kg}$	ml/min.kg	0.97	0.68-1.4	22%	1.0	0.6-2.4	37%
dose	MAC-hr	1.45	1-3	42%	1.27	0.2-3	65%
duration	hr	2.40	1-4	37%	2.65	0.6-8.2	61%
MAC		0.62	0.4-1	26%	0.48	0.1-'0.9	37%
$C_{\text{max}}$	$\mu\text{M}$	28.00	11-50	42%	24.12	7.5-45	47%
$T_{\text{max}}$	hr	1.95	0-13	179%	1.32	-0.8 - 12	237%
$\text{AUC}_{0-\infty}$	$\mu\text{M}\cdot\text{hr}$	762.32	282-1607	50%	779.26	95 - 3732	109%
$\text{AUC}_{0-\infty}/\text{dose}$	$\mu\text{M}\cdot\text{hr}/(\text{MAC}\cdot\text{hr})$	575.55	217-1027	46%	646.74	176 -	60%
$t_{1/2}$	monophasic (hr)	21.61	9 - 42	53%	27.25	8.4 - 73	84%
	n	8			11		
$t_{1/2}$	$\alpha$ -phase (hr)	4.60	1 - 9	72%	5.83	1.7 -16	94%
$t_{1/2}$	$\beta$ -phase (hr)	26.84	20 - 44	38%	24.30	18 - 33	19%

In 525 elderly patients (defined as having an age greater than 65 years) underwent statistically longer surgeries than did the young patients, although half of the elderly patients underwent cardiac surgery and sevoflurane exposure may have been discontinued during the surgical procedure. The mean of the observed maximum fluoride concentration,  $C_{max}$ , was 23.9  $\mu\text{M}$  (range 8.7-56.2 $\mu\text{M}$ ) in the elderly group and 33.2 $\mu\text{M}$  (range 9.8-77.5 $\mu\text{M}$ ) in the non-elderly group. The half-life was almost doubled in the elderly group compared with the non-elderly group (harmonic mean non-elderly  $t_{1/2}$ =8.2hr, 190%CV, range 0.6-72.7hr; harmonic mean elderly  $t_{1/2}$ =15.1hr, 98%CV range 4.4-45.3) a consequence of reduced renal function. Half-life estimates for the non-elderly group were similar to estimates obtained in other studies with similar sampling regimens and where sevoflurane was administered at similar doses. Demographics and parameter estimates for the elderly and non-elderly group are displayed below.

**Table 9** Fluoride ion parameter estimates and demographics for elderly and non-elderly groups compared in 525

525	non-elderly		range	elderly		range
	mean	cv		mean	cv	
N	108			31		
Age (yr)	43	28%	19-64	72	8%	65-87
Weight (kg)	89	32%	50-218	76.7	18%	50-108
Duration (hrs)	2.91	42%	1-7.15	3.53	40%	1-5.61
MAC	0.56			0.38		
Dose (MAC-hr)	1.62	54%	0.43-5.68	1.34	41%	0.26-2.55
$C_{max}$ ( $\mu\text{M}$ )	33.2	32%	9.8-77.5	23.9	53.50%	8.7-56.2
$t_{1/2}$ (hr) (harmonic mean)	8.2	190%	0.6-72.7	15.1	98%	4.4-45.3
n	80			12		

### 7.8.2.5.3 Renally impaired populations

The effect of renal impairment on fluoride pharmacokinetics following sevoflurane administration was assessed in two studies of renally-impaired patients undergoing elective surgical procedures (SEVO-92-002 and 529).<sup>20, 21</sup> Sevoflurane was administered in oxygen/nitrous oxide (Study SEVO-92-002) or 100% oxygen (529) to patients with renal insufficiency (serum creatinine  $\geq 1.5$  mg/dL) undergoing elective surgical procedures of up to 3 hours (SEVO-92-002) or 1 to 6 hours (529) in duration. Fluoride half-life was prolonged in renally impaired patients compared with those patients with normal renal function (mean non-renal  $t_{1/2\text{monophasic}} = 15.4$  hr, 45% CV, range 5.3-36 hr; mean renally impaired  $t_{1/2\text{monophasic}} = 34.9$  hr, 37% CV, range 15.1-16.1 hr). Mean fluoride  $C_{\text{max}}$  values were comparable between the two groups (mean non-renal  $C_{\text{max}} = 24.6$   $\mu\text{M}$ , 43% CV, range 11-62  $\mu\text{M}$ ; mean renal  $C_{\text{max}} = 26.14$   $\mu\text{M}$ , 41% CV, range 10-52  $\mu\text{M}$ ).

Comparison of the renally-impaired sevoflurane-treated patients and a demographically matched subset of patients with normal renal function who received sevoflurane in Study SEVO-92-003 indicated that the two populations were comparable with respect to age, weight, height, and sevoflurane dose. The duration of anesthesia was shorter for normal patients (2 hrs vs 2.5 hrs). While there was no difference between the normal and renally-impaired patients in dose-adjusted  $C_{\text{max}}$ , patients with renal impairment had significantly greater values for total AUC, dose-normalized AUC and terminal disposition half-life. The mean clearance determined from the ratio of dose/AUC<sub>0- $\infty$</sub>  for this population was approximately twice that compared with normal patients in SEVO-92-003. Parameters and demographics for SEVO-92-012 and SEVO-92-003 are displayed in Table 11.

### 7.8.2.5.4 Hepatically impaired populations

The effect of hepatic impairment on sevoflurane metabolism was assessed in Study 530.<sup>22</sup> Following intravenous induction, sevoflurane was administered in 100% oxygen or up to 70% nitrous oxide in ASA Class II or III patients with hepatic impairment (Child-Pugh Class A or B) undergoing elective surgical procedures of 1-6 hours duration. Blood samples for determination of inorganic fluoride concentrations were collected pre-operatively, during sevoflurane administration, and post-anesthesia. The pharmacokinetic parameter results are summarized in Table 10.

Peak fluoride concentrations were similar to those observed in studies of patients with normal hepatic function (normal  $C_{\text{max}} = 24.6$   $\mu\text{M}$ , 43% CV, range 11-62  $\mu\text{M}$ ; hepatic  $C_{\text{max}} = 31$   $\mu\text{M}$ , 30% CV, range 17-44  $\mu\text{M}$ ). However, fluoride half-life was prolonged relative to that observed in normal patients (mean normal  $t_{1/2\text{monophasic}} = 15.4$  hr, 43% CV, range 5.3-36 hr; mean hepatically impaired  $t_{1/2\text{monophasic}} = 33.4$  hr, 38% CV range 22-47). This may be a result of the effects of hepatic impairment on renal elimination of inorganic fluoride. It has been suggested that hepatic insufficiency may lead to intra-renal vasoconstriction, stimulation of the renin-angiotensin system, and reduced renal blood flow.<sup>48</sup> The elevation in dose-normalized AUC can be explained by the longer fluoride half-life in these patients with hepatic impairment.

**Table 10** Non compartmental parameter estimates and demographics for patients in hepatic failure study (530).

-530		mean	cv	range
N		8		
age	yr	54.75	21%	42-79
dose	MAC-hr	2.22	74%	0.53-4.9
MAC		0.58	38%	0.27-1.02
duration	hr	3.61	63%	1.3-8.23
$C_{max}$	$\mu M$	30.59	30%	16.5-43.5
$AUC_{inf}/dose$	$\mu M \cdot hr/MAC-hr$	1405.70	65%	261-2459
$t_{1/2}$ (mono)	hr	33.4	38	21.5-47
n		4		
$t_{1/2}$ (alpha)	hr	1.5	-	-
$t_{1/2}$ (beta)	hr	18.8	-	-
n		1		

Table 11 Comparison of demographics and parameter estimates determined in normal and renally impaired patients; (SEVO-92-003 & SEVO-92-012).

	SEVO-92-002				SEVO-92-003			
	Renally impaired				Normals			
		mean	CV	range	mean	N	CV	range
N		21						
age	yrs	67.43	23%	29-83	48.12	73	38%	18-92
Cr	mg/dL	2.23	45%	1.4-5	nd	-	-	-
CL <sub>r</sub>	ml/min	35.24	42%	15-66	nd	-	-	-
Dose	MAC-hr	1.01	45%	0.2-2.06	1.08	73	71%	0.2-3.9
duration	hr	2.52	37%	0.6-4	2.07	73	51%	0.76-5.9
MAC		0.41	27%	0.18-.70	0.50	73	35%	0.13-0.89
C <sub>max</sub>	μM	26.14	41%	9.6-51.8	24.64	70	43%	11.1-62.8
T <sub>max</sub>	hr	1.1	218%	-0.4 - 8.2	1.49	68	186%	-1.25 -14.5
AUC <sub>0-∞</sub>	μM-hr	1071.59	51%	274-2296	474.03	65	94%	116-3282
AUC/dose	μM-hr/MAC-hr	1259.40	69%	423-3931	494.94	65	58%	178-1737
Dose*1000/AUC <sub>0-∞</sub>	MAC-hr/μM-hr	1.12	54%	0.25-2.4	2.59	65	47%	0.57-5.60
t <sub>1/2</sub> (monophase)	hr	34.86	37%	15.1-61.1	15.38		45%	5.3-36
n		14			43.00			
t <sub>1/2</sub> (alpha)	hr	3.19	66%	0.4-7.2	2.73		67%	0.2-8.4
t <sub>1/2</sub> (beta)	hr	37.17	35%	21.7-53.7	23.15		39%	9.5-48
n		7			20			

not determined

### 7.8.2.5.5 Neonate populations

In Study SEVO-92-011, maternal and neonatal serum fluoride determinations following sevoflurane administration were obtained in patients undergoing elective cesarean section.<sup>12</sup> Following intravenous induction, sevoflurane was administered in oxygen/nitrous oxide. Maternal blood samples were obtained pre-operatively and 24 hours post-anesthesia. Arterial umbilical cord samples were collected at birth. Mean neonate fluoride concentrations at birth relative to the anesthetic dose are displayed in Table 12.

**Table 12** Maternal and neonatal maximum serum fluoride concentrations following sevoflurane administration in patients undergoing cesarean section (SEVO-92-011).

SEVO-92-011					
		N	mean	cv	range
age	yr	27	26.56	19%	17-37
Dose	MAC-hr	27	0.42	35%	0.2-.80
Duration	hr	27	0.90	30%	0.57-1.57
MAC		27	0.47	16%	0.25-0.57
Duration, neonate exposure	hr	27	0.15	46%	0.05-0.33
conc at 24 hr	$\mu$ M	25	3.54	35%	1.7-7.7
umbilical cord conc after birth	$\mu$ M	26	2.31	47%	0.9-0.63

### 7.8.2.5.6 Obese populations

The effect of obesity and age on sevoflurane defluorination was investigated in study 525. This was a parallel group, multicenter trial conducted in ASA 1, 11 and 111 patients administered sevoflurane or isoflurane while undergoing regularly scheduled surgery. Obesity was defined as 66 lbs. above the ideal weight. Obese patients and non-obese patients underwent

surgeries of virtually the same duration. The mean of the observed maximum fluoride concentration,  $C_{max}$ , was  $38.0 \mu\text{M}$  (29%CV, range 23.0-77.5 $\mu\text{M}$ ) in the obese group and  $28.8\mu\text{M}$  (39%CV, range 8.7-62.0 $\mu\text{M}$ ) in the normal weight group. This difference was statistically significant. The half-life was slightly prolonged in the obese group (mean  $t_{1/2}$ =11.3 hr, 125%CV, range 2.1-72.7) compared with the normal weight group (mean  $t_{1/2}$ =8.3 hr, 205%CV, range 0.6-45.3) but was not statistically significant. Half-life estimates were similar to estimates obtained in other studies with similar sampling regimens and where sevoflurane was administered at similar doses. Demographics and parameter estimates for the obese and non-obese group are displayed below.

Table 13 Fluoride ion parameter estimates and demographics for obese and non-obese groups compared in 525.

525	normal weight			obese		
	mean	cv	range	mean	cv	range
N	104			35		
Age (yr)	51	33%	19-87	45	28%	24-73
Weight (kg)	75.7	19%	104-117.1	117.5	25%	88.5-217.9
Duration (hrs)	3.05	43%	1.75-7.15	3.05	40%	0.58-6.8
MAC †	0.49	-	-	0.57		
Dose (MAC-hr)	1.51	52%	0.26-5.68	1.71	52%	0.65-4.58
$C_{max}$ ( $\mu\text{M}$ )	28.8	39%	8.7-62.0	38	286	23.1-77.5
$t_{1/2}$ (hr) ††	7.9	205%	0.6-45.3	11.3	125%	2.1-72.7

† mean MAC determined by duration/dose

†† mean of monophasic and  $\beta$ -phase half-lives

## 8 INHIBITION OF CYTOCHROME P450 2E1 BY DISULFIRAM

Twenty-two patients undergoing elective surgical procedures were randomized to receive a single dose of 500 mg of disulfiram on the evening prior to surgery (n=12) or to be an untreated control (n=10). Following intravenous induction, sevoflurane was administered in oxygen/air or oxygen/nitrous oxide for 3 to 4 hours. Blood samples for determination of inorganic fluoride, sevoflurane and HFIP concentrations were obtained pre-operatively, during sevoflurane

administration, and post-anesthesia. Urine samples for determination of inorganic fluoride and HFIP concentration were obtained from 12 hours prior to surgery up to 96 hours post-surgery. The pharmacokinetic parameter results for inorganic fluoride are summarized below. Disulfiram administration significantly inhibited the production of fluoride and HFIP via sevoflurane metabolism. The mean fluoride  $C_{max}$  in the disulfiram-treated group was 49% of that in the control group, and the mean serum fluoride  $AUC_{0-\infty}$  in the disulfiram-treated group was 26% of that in the control group. Patients generally demonstrated a biphasic serum fluoride concentration-time profile. The mean fluoride half-lives were 8.4 and 21.4 hours, respectively, for patients in the disulfiram and control groups. Urine samples for determination of inorganic fluoride and HFIP concentration were obtained from 12 hours prior to surgery up to 96 hours post-surgery. The pharmacokinetic parameter results for inorganic fluoride are summarized below. Disulfiram administration significantly inhibited the production of fluoride and HFIP via sevoflurane metabolism.

**Table 14** Fluoride ion pharmacokinetic parameter estimates from disulfiram study

SEVO-93-037	control			disulfiram		
	mean	CV	range	mean	CV	range
MAC	1.27	52%	1.16-1.39	1.3	27%	1.25-1.39
duration (hr)	2.9	9%	2.25-3.1	2.85	9%	2.3-3
Dose (MAC-hr)	3.7	10%	2.96-4.19	3.72	3%	2.97-4.16
$C_{max}$ (um)	36.2	34%	23.3-61.5	17.6	30%	10.1-24.0
$\Delta C_{max}$ ( $\mu M$ )	34	37%	22-60	15.9	32%	8.3-22.4
$t_{1/2}$ (hr) (harmonic mean)	21.4	41%	13.1-39.8	8.4	60%	4.5-31.8
$AUC_{0-\infty}$	1113	46%	442-1973	289	98%	105-869
amt excreted (96hrs) ( $\mu M$ )	3949	45%	1534-6948	1241	70%	338-3046
amt excreted from sevoflurane ( $\mu M$ )	3305	52%	1207-6230	876	92%	131-2578
renal clearance (ml/min)	52	27%	36-72	40	37%	22-65

## 9 KINETICS OF COMPOUND A

Sevoflurane in the presence of CO<sub>2</sub> absorbants produces 2 degradation products in the clinical setting. These have been identified as Compound A and B. High concentrations of Compound A have been associated with renal injury in rats. Three hours exposure to compound A at 330-360 ppm causes death (LC<sub>50</sub>) in rats. The kinetics of compound A in humans and the potential for toxicity in humans under conditions of low flow and long anesthetic exposure is undetermined at present and this is an issue of concern.

Compound A concentrations were measured in one pharmacokinetic study (NDA 20-478) submitted in the pharmacokinetics section of the NDA. sevoflurane was administered via a low flow circle absorption delivery system. Flow rate, temperature of the CO<sub>2</sub> absorbent canister, or dose administered were not indicated. Sodalime was the absorbent used for 12 subjects and baralyme for 8 subjects. The mean maximum inspired and expired concentrations were approximately 7ppm (CV=30%, range 3-15ppm) and 4 ppm (CV=70%, range 1-7ppm) respectively for the sodalime group. The mean maximum inspired and expired concentrations for the baralyme group were approximately 17ppm (CV=120%, range 2.6-61) and 11 ppm (CV=113%, range 3-40ppm) respectively. In one patient in the baralyme group the maximum observed concentration of compound A was approximately 60ppm. Other investigators (Bito and Ikeda have reported concentrations of 19.5 ppm (range 12.0-30.0ppm) with soda lime and 27.9 (range 18.3-37.8 ppm) with baralyme at a fresh gas flow rate of 1L/min. Figures of individual compound A

Figure 20 Individual compound A concentrations; (sodalime adsorbent).

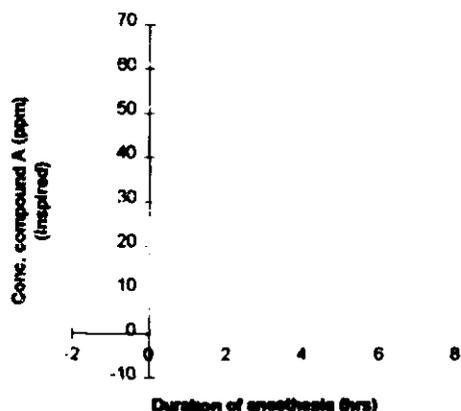
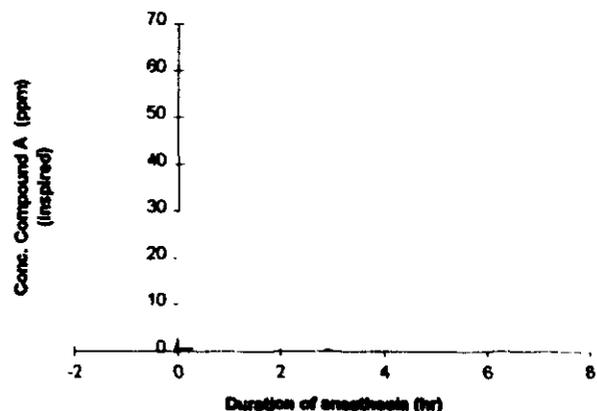


Figure 21 Individual compound A concentrations; (baralyme adsorbent).



concentrations as a function of time for the baralyme and sodalime groups are displayed below.

**10 APPENDIX 1: References**

1. 520: A Phase II, randomized, open-label study to compare the safety and tolerability of sevoflurane and isoflurane in ASA Class I and II patients. (Drug Metabolism Report No. 1) Report No. R&D/93/523, July 29, 1993.
2. 522: A Phase II, open-label study to evaluate the pharmacological effects of sevoflurane administered in a low-flow, closed circuit, anesthetic delivery system in ASA Class I and II patients. (Drug Metabolism Report No. 2) Report No. R&D/93/524, July 29, 1993.
3. 536: A Phase II, single center, randomized, open-label study to evaluate the renal concentrating ability of healthy male volunteers who are administered sevoflurane or enflurane. (Drug Metabolism Report No. 7) Report No. R&D/93/761, October 29, 1993.
4. Cato A. Study SEVO-93-044: Comparison of serum fluoride concentrations during and after administration of sevoflurane and enflurane in: A Phase I, single center, open-label study evaluating the urine concentrating ability of healthy male volunteers following administration of 3, 6, and 9 MAC hours of sevoflurane. (Drug Metabolism Report No. 15) Report No. R&D/94/368, May 23, 1994.
5. Karol MD. Study SEVO-92-003: A Phase III, multicenter, open-label randomized, comparative study evaluating the effect of sevoflurane versus isoflurane in the maintenance of anesthesia in adult ASA Class I, II and III inpatients. (Drug Metabolism Report No. 12) Report No. R&D/94/224, April 7, 1994.
6. Karol MD. Study SEVO-92-005: A Phase III, multi-center, open-label, randomized, comparative study evaluating the effect of sevoflurane versus enflurane in the maintenance of anesthesia in adult ASA Class I, II, III inpatients. (Drug Metabolism Report No. 23) Report No. R&D/94/451, June 27, 1994.
7. 525: A Phase III, multicenter, randomized, open-label study to compare the safety and tolerability of sevoflurane versus isoflurane administered with nitrous oxide and oxygen in ASA Class I, II and III patients. (Drug Metabolism Report No. 6) Report No. R&D/93/759, October 29, 1993.

8. 523: A Phase II, open-label study to compare the epinephrine-induced arrhythmogenic effect of sevoflurane and isoflurane in patients undergoing transsphenoidal hypophysectomy surgery. (Drug Metabolism Report No. 3) Report No. R&D/93/586, August 17, 1993.
9. 528: A Phase III, randomized, open-label study to compare the safety and tolerability of sevoflurane versus isoflurane administered with nitrous oxide in patients undergoing neurosurgery. (Drug Metabolism Report No. 20) Report No. R&D/94/421, May 23, 1994.
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11. 531: A Phase III, multi-center, open-label study to evaluate the effects of repeat exposures of sevoflurane in ASA Class I, II and III patients. (Drug Metabolism Report No. 24) Report No. R&D/94/452, June 6, 1994.
12. Rynkiewicz K, Karol MD. Study SEVO-92-011: A Phase III, multi-center, open-label, randomized, comparative study evaluating the effect of sevoflurane versus isoflurane regimen in ASA Class I and II inpatients undergoing elective cesarean section. (Drug Metabolism Report No. 18) Report No. R&D/94/387, May 20, 1994.
13. 532: The minimum alveolar concentration (MAC), and maintenance and recovery characteristics of sevoflurane in pediatric patients. (Drug Metabolism Report No. 8) Report No. R&D/93/762, October 29, 1993.
14. Karol MD. Study SEVO-92-001: A Phase III, single center, open-label, randomized, comparative study evaluating the effect of sevoflurane versus halothane on hepatic metabolism in the induction and maintenance of anesthesia in pediatric inpatients. (Drug Metabolism Report No. 5) Report No. R&D/93/738, October 29, 1993.

15. Rynkiewicz K, Karol MD. Study SEVO-92-008: A Phase III, multi-center, open-label, randomized, comparative study evaluating the effect of sevoflurane versus halothane in the induction and maintenance of anesthesia in pediatric ASA Class I and II inpatients. (Drug Metabolism Report No. 17) Report No. R&D/94/386, May 24, 1994.
16. Rynkiewicz K, Karol MD. Study SEVO-92-015: A Phase III, multi-center, open-label study evaluating the effect of multiple exposure to sevoflurane for the maintenance of anesthesia in pediatric ASA Class I, II and III inpatients. (Drug Metabolism Report No. 21) Report No. R&D/94/443, May 25, 1994.
17. 533: A Phase II, randomized, open-label study to compare the safety and efficacy of sevoflurane versus halothane administered with nitrous oxide and oxygen in ASA Class I and II pediatric patients. (Drug Metabolism Report No. 4) Report No. R&D/93/691, September 30, 1993.
18. 534: A Phase III, randomized, open-label study to compare the safety, tolerability and recovery characteristics of sevoflurane versus halothane with nitrous oxide and oxygen in ASA Class I and II pediatric patients undergoing ambulatory surgery. (Drug Metabolism Report No. 9) Report No. R&D/93/854, November 23, 1993.
19. Karol MD. Study SEVO-92-012: A Phase III, multi-center, open-label, randomized, comparative study evaluating the use of sevoflurane versus isoflurane in the maintenance of anesthesia in elderly, ASA Class I, II and III inpatients. (Drug Metabolism Report No. 13) Report No. R&D/94/306, April 29, 1994.
20. Karol MD. Study SEVO-92-002: A Phase III, multi-center, open-label, randomized, comparative study evaluating the effect of sevoflurane versus enflurane in the maintenance of anesthesia in renal compromised ASA Class II and III adult inpatients. (Drug Metabolism Report No. 22) Report No. R&D/94/448, May 31, 1994.
21. -529: A Phase III, multi-center, randomized, open-label study to compare the safety and tolerability of sevoflurane versus isoflurane in ASA Class II and III patients with renal insufficiency. (Drug Metabolism Report No. 11) Report No. R&D/94/223, March 24, 1994.

22. 530: A Phase III, multicenter, randomized, open-label study to determine the degree of metabolism of sevoflurane versus isoflurane in hepatically impaired patients. (Drug Metabolism Report No. 14) Report No. R&D/94/350, May 5, 1994.
23. Karol MD. Study SEVO-92-014: A Phase I, single center, open-label, randomized study evaluating the effect of phenobarbital on the defluorination of sevoflurane in healthy male volunteers. (Drug Metabolism Report No. 19) Report No. R&D/94/396, May 24, 1994.
24. Karol MD. Study SEVO-93-037: A Phase II, single center, open-label, randomized study identifying the role of cytochrome P450 2E1 in clinical sevoflurane defluorination in adult inpatients undergoing elective surgery. (Drug Metabolism Report No. 25) Report No. R&D/94/557, June 29, 1994.
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26. Shiraishi Y, Ikeda K. Uptake, elimination and biotransformation of volatile anesthetics in humans: A comparative study of sevoflurane with halothane, enflurane, and isoflurane. Unpublished report, Hamamatsu University, October 1986.
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VACCARI  
DEC 6 1994

PILOT DRUG EVALUATION STAFF  
Pharmacology and Toxicology Review

**NDA:** 20-478

**IND:**

**Submission:** NDA Dated: July 8, 1994  
Received by CDR: July 11, 1994  
Received by HFD 007: July 13, 1994  
Received by Reviewers: July 18, 1994  
Review Completed: Dec. 6, 1994  
Reviewers: M. Anwar Goheer, Ph.D. & Almon W. Coulter, Ph.D.

**Sponsor:** Abbott Laboratories  
One Abbott Park Road, D389, AP30  
Abbott Park, Illinois 60064

**Information to be conveyed to the sponsor:** Yes 1

**Drug:** International Non-proprietary Name (INN): Sevoflurane (Sevorane™)

**Structural Formula:** 
$$\begin{array}{c} \text{F}_3\text{C} \backslash \\ \text{CH-OCH}_2\text{F} \\ \text{F}_3\text{C} / \end{array}$$

**Molecular Formula:** C<sub>4</sub>H<sub>7</sub>F<sub>7</sub>O

**Molecular Weight:** 200.05

**Chemical Name:** Fluoromethyl 2,2,2-trifluoro-1(trifluoromethyl) ethyl ether

**British Approved Name:** 1,1,1,3,3,3-hexafluoro-2-fluoromethoxypropane

**Other Name:** Sevofrane<sup>®</sup> in Japan

**Chemical Abstract Number (CAS):** 28523-86-6

**Drug Manufacturer:** The drug substances is manufactured at:

The finished product is manufactured At:

Abbott Laboratories,  
Hospital Products Division  
Highway 301 North  
Rocky Mount, NC 27801

**Dosage Form:** Liquid



NDA 20478

ULTANE

3 OF 4

**Main Component/Gas Partition Coefficients at 25 °C:**

- Conductive rubber
- Butyl rubber
- Polyvinyl chloride
- Polyethylene

**Solubility:** Sevoflurane is miscible with ethanol, ether, chloroform and petroleum benzene and it is slightly soluble in water.

**Flammability** - Non-flammable and nonexplosive as defined by the requirements of International Electrotechnical Commission (IEC).

Physicochemical properties of Sevoflurane and widely-used volatile anesthetics are given below:

Physicochemical Properties	Halothane	Enflurane	Isoflurane	Desflurane	Sevoflurane
Molecular Weight	197.5	184.5	184.5	168.0	200.1
Boiling Point (°C) (at 760 mm Hg)	49-51	56.5	48.6	22.8	58.6
Specific Gravity (25 °C/4 °C)	1.86	1.52	1.50	1.50	1.53
Vapor Pressure (mm Hg @ 20°C)	243	175	238	669	157
Blood/Gas Partition Coefficient	2.35	1.91	1.4	0.42	0.63
Oil/Gas Partition Coefficient	224	96	91	18.7	47
Reacts with Metals	Yes	No	No	No	No
UV Light Stability	No	Stable	Stable	NA	Stable
Soda Lime ® Stability	No	Stable	Stable	Stable	No
Antioxidant Needed	Thymol	No	No	No	No
Min. Flammable Conc. in 100% O <sub>2</sub>	4.8 %	5.8%	7.0%	NA	7.5 %

NA = Not available

**Degradation mechanism of Sevoflurane and**

**in contact with CO<sub>2</sub> absorbants:**

adds to Compound A to form Compound B:

By comparison,

Preclinical Studies:

Previously Reviewed submissions:

- (1) The following studies were reviewed by Clyde Oberlander on Feb 27, 1986 under IND
  - (i) Preliminary study with sevoflurane in cynomolgus monkeys.
  - (ii) An acute inhalation study of sevoflurane in cynomolgus monkeys.
  - (iii) An eight week inhalational toxicity study of sevoflurane in cynomolgus monkeys.
  - (iv) Eight week inhalational subacute toxicity study of sevoflurane in rats.
  
- (2) The following additional preclinical data were evaluated by Clyde Oberlander under IND and are summarized in IND dated Feb. 27, 1986.
  - (a) Pharmacology.
    - (i) Inhalational anesthetic activity in mice.
    - (ii) Drug interaction studies.
    - (iii) Cardiac sensitizing properties in dogs
      - Acute epinephrine studies
      - Subacute epinephrine studies
      - Pressoramine experiments

- (iv) Synthetic impurities and reaction products
  - Synthetic impurities
  - Soda lime reaction product.
- (v) Blood glucose studies in dogs.

(b) Pharmacokinetics

- (i) Fluoride excretion - rats
- (ii) Metabolism by rat hepatic microsomes of fluorinated ether anesthetics following ethanol consumption.
- (iii) Metabolism by rat hepatic microsomes of fluorinated ether anesthetics following isoniazid administration.
- (iv) Renal effects and metabolism of sevoflurane in Fischer 344 rats.
- (v) A comparison of renal effects and metabolism of sevoflurane and methoxyflurane in enzyme-induced rats.
- (vi) Biotransformation of sevoflurane in dogs and rats.
- (vii) Pharmacokinetic and metabolic studies in dogs.

(c) Toxicology:

Acute Toxicity

- (i) Acute toxicity studies in four species.
- (ii) Preliminary study with sevoflurane in cynomolgus monkeys.
- (iii) Acute inhalation study of sevoflurane in cynomolgus monkeys

Subacute Toxicity

- (i) Eight week inhalational subacute toxicity study of sevoflurane in rats.
- (ii) Subacute toxicity in dogs.
- (iii) Subacute toxicity in primates
- (iv) Eight-week inhalation toxicity study of sevoflurane in cynomolgus monkeys

(d) Mutagenicity studies.

- (i) Mutagenicity of experimental inhalational anesthetic agents: sevoflurane, synthane, dioxychlorane, and dioxylflurane.
- (ii) Variations in onset of porcine malignant hyperthermia
- (iii) Thermoregulatory defect in rats during anesthesia.

(e) Special Study:

- (i) Eye irritation - rabbit

Studies Reviewed:

Pharmacology Studies:

A. Neuropharmacological Studies:

1. The effect of Sevoflurane on central blood flow, cerebral metabolic rate for oxygen, intracranial pressure, and the electroencephalogram are similar to those of Isoflurane in rabbit. Scheller

- et al, *Anesthesiology* 1988;68:548-51.
2. Effects of Sevoflurane on the intracranial pressure in dogs.
  3. Effects of Sevoflurane on electroencephalographic activity in rats-compared with Enflurane and Halothane.
  4. The effect of Sevoflurane on somatically induced sympathetic reflexes. Yanase et al, *J Anesth* 1988;2:272-5.
  5. Effect of Sevoflurane on central nervous system.
  6. The effect of Sevoflurane, a new inhalation anesthetic, on spinal reflex action potentials.
  7. Central effects of the new inhalation anesthetic Sevoflurane - effects on EEG arousal and recruiting responses and hippocampal after-discharge.
  8. Clinical and experimental studies on the potentiation of neuromuscular blocking effects of vecuronium and pancuronium by Sevoflurane.
  9. General pharmacological study of HFIP - observation of the effects of HFIP on the central nervous system and general condition.
  10. General pharmacological study of HFIP - effect of HFIP on spontaneous motor activity in mice.

#### B. Cardiovascular/Respiratory Studies

1. Comparison of the epinephrine-induced arrhythmogenic effect of Sevoflurane with Isoflurane and Halothane. S. Imamura and K. Ikeda, *J Anesth* 1987;1:62-8.
2. Cardiovascular interaction between Sevoflurane and Nicardipine in open chest dogs. Iwatsuki et al, *J Anesthesia* 1988;2:146-53.
3. Arrhythmogenic threshold of epinephrine during Sevoflurane, Enflurane and Isoflurane anesthesia in dogs. Hayashi et al, *Anesthesiology* 1988; 69:145-7.
4. The comparative cardiovascular effects of Sevoflurane with Halothane and Isoflurane. Kazama et al, *J Anesth* 1988;2:63-8.
5. Effect of inhalation anesthetic Sevoflurane on atrioventricular conduction in dogs.
6. The effect of Sevoflurane on regional myocardial blood flow in ischemic heart.
7. Influence on hemorrhagic hypotension under Sevoflurane and Halothane anesthesia on renal circulation and metabolism.
8. Effects of Halothane, Isoflurane, Sevoflurane and Enflurane on portal venous pressure in the isolated perfused rat liver.
9. Effects of Sevoflurane and Isoflurane on cardiac and coronary dynamics in chronically instrumented dogs. Bernard et al, *Anesthesiology* 1990; 72:659-62.
10. Sevoflurane anesthesia: compatibility with morphine, atropine, succinylcholine, lidocaine and pentothal.
11. Synthetic organic chemicals (comparison of arrhythmogenic effects evoked by various pressoramines under Halothane or Sevoflurane anesthesia in dogs.
12. Comparative in vivo evaluation of Sevoflurane, Halothane, Methoxyflurane and Isoflurane in Sprague-Dawley rats.
13. The effects of Sevoflurane (BAX 3084) and Halothane on arterial blood pressure and spontaneous heart rate in dogs.
14. Sevoflurane causes direct negative inotropic and lusitropic effects in chronically instrumented dogs.
15. Sevoflurane and coronary steal.
16. MAC value of a new inhalation anesthetic agent Sevoflurane (MR6S4) in mice and rats.
17. MAC value of Sevoflurane in rabbits.
18. Determination of the MAC of Sevoflurane, a new inhalation anesthetic, in rabbits - additional information concerning the 95% confidence limits of MAC.
19. The respiratory effects of Sevoflurane in dogs.
20. Comparison of MAC and the rate of rise of alveolar concentration of Sevoflurane with Halothane and Isoflurane in the dog. T. Kazama and K. Ikeda, *Anesthesiology* 1988;

68:435-437.

21. The minimum alveolar concentration of Sevoflurane in cats. Doi et al, *J Anesthesia* 1988; 2:113-114.
22. MAC of Sevoflurane in humans and the New Zealand white rabbit. Scheller et al, *Can J Anesth* 1988; 35:153-156
23. The minimum alveolar concentration (MAC) and hemodynamic effects of Halothane, Isoflurane and Sevoflurane in newborn swine.

#### C. Genitourinary Studies:

1. Effect of Sevoflurane on isolated rat uterus and vas deferens.

#### D. Miscellaneous Physiological Studies:

1. General pharmacological studies of Sevoflurane.
2. Variations in onset of porcine malignant hyperthermia. G.A. Gronert and J.H. Milde, *Anesth Analg* 1981; 60:499-503
3. Malignant hyperthermia induction in susceptible swine following exposure to Sevoflurane.
4. Sevoflurane effect on control pigs and Halothane comparative effect in triggering malignant hyperthermia in MHS pig #15, 9, 17.
5. Study on the hemolytic effect of Sevoflurane using human and rabbit erythrocytes.
6. Hepatic effects of Sevoflurane - the changes of drug metabolizing enzymes and morphic features.
7. Thermoregulatory defect in rats during anesthesia. Hitt et al, *Anesthesia Analgesia Curr Res* 1977; 56:388-394.

#### Drug Metabolism

1. The blood concentration of Sevoflurane after inhalation in rats. Tamada et al, Maruishi Pharmaceutical Co., Ltd. Report, November 1986.2658/7
2. Time course of free HFIP and HFIP glucuronide concentrations in blood after intravenous administration of HFIP to rats. Yoshimura et al, Maruishi Pharmaceutical Co., Ltd. Report, August 1988.
3. Elimination kinetics of Sevoflurane and Halothane from blood, brain and adipose tissue in the rat. Stern et al, *Anesthesia and Analgesia* 1990; 71:658-664.
4. General anesthetic distribution in rat brain; <sup>19</sup>F-MRI of Sevoflurane. Xu et al, *Anesthesiology* 79:A414, 1993.
5. Ionchromatographical analysis of a glucuronide as a Sevoflurane metabolite. Fujii et al, *Hiroshima J Anesthesia* 23:3-7, 1987.
6. Excretion of a glucuronide in bile as a Sevoflurane metabolite during Sevoflurane anesthesia. Fujii et al, Department of Anesthesiology, unpublished report, August 1985.
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8. Inhibitory effects of deuterium substitution on the metabolism of Sevoflurane by the rat. Baker et al, *Drug Metabolism and Disposition* 21:1170-1171, 1993.
9. Metabolism of Synthane: Comparison with in vivo and in vitro defluorination of other halogenated hydrocarbon anesthetics. Mazze et al, *Br J Anesthesiology* 51:839-844, 1979.
10. Effect of phenytoin (DPH) treatment on Methoxyflurane metabolism in rats. Caughey et al, *J Pharm Exp Therapeutics* 210:180-185, 1979.

11. Effects of isoniazid treatment on selected hepatic mixed-function oxidases. S.A. Rice and R.E. Talcott, *Drug Metabolism and Disposition* 7:260-262, 1979.
12. Metabolism by rat hepatic microsomes of fluorinated ether anesthetics following Isoniazid administration. Rice et al, *Anesthesiology* 53:489-493, 1980.
13. Metabolism by rat hepatic microsomes of fluorinated ether anesthetics following ethanol consumption. Rice et al, *Anesthesiology* 58:237-241, 1983.
14. Biotransformation of Sevoflurane in male Sprague-Dawley rat liver slices. Payne et al, *ISSX Proceedings* 4:168, 1993.
15. Biotransformation of Sevoflurane in dogs and rats. Martis et al, *Anesthesia and Analgesia* 60:186-191, 1981.
16. Preliminary pharmacokinetic and metabolic studies of Sevoflurane in dogs. L. Martis and E.F. Woods, Travenol Laboratories Research Report, February 9, 1978.
17. A new inhalation anesthetic. Wallin et al, *Anesthesia and Analgesia* 54:758-765, 1975.
18. Comparative in vivo evaluation of Sevoflurane, Halothane, Methoxyflurane and Isoflurane in Sprague-Dawley rats (IND)
19. A comparison of the renal effects and metabolism of Sevoflurane and Methoxyflurane in enzyme-induced rats. Cook et al, *Anesthesia and Analgesia* 54:829-835, 1975.
20. Renal effects and metabolism of Sevoflurane in Fisher 344 rats: An in vivo and in vitro comparison with Methoxyflurane. Cook et al, *Anesthesiology* 43:70-77, 1975.
21. Renal function after Sevoflurane or Enflurane anesthesia in the Fisher 344 rat. Malan et al, *Anesthesia and Analgesia* 77:817-821, 1993.
22. Metabolic and toxicologic studies with Enflurane in Swiss/ICR mice. Baden et al, *J Environmental Pathology and Toxicology* 4:293-303, 1980.
23. Sevoflurane is biotransformed by guinea pig liver slices but causes minimal cytotoxicity. Ghantous et al, *Anesthesia and Analgesia* 75:436-440, 1992.
24. Sevoflurane biotransformation and hepatotoxicity in the guinea pig. Lind et al, *Anesthesiology* 71:A310, 1989.
25. Dose-related Sevoflurane metabolism to inorganic fluoride in rabbits. Hossain et al, *Hiroshima J Med Sci*, 40:1-7, 1991.
26. Ethanol-inducible cytochrome P450 in rabbits metabolizes Enflurane. Hoffman et al, *British Journal of Anesthesia* 63:103-108, 1989.
27. Comparison of MAC and the rate of rise of alveolar concentration of Sevoflurane with Halothane and Isoflurane in the dog. T. Kazama and K. Ikeda, *Anesthesiology* 68:435-437, 1988.
28. Pharmacokinetics of Desflurane, Sevoflurane, Isoflurane, and Halothane in pigs. Yasuda et al, *Anesthesia and Analgesia* 71:340-348, 1990.
29. Volatile anesthetics compete for common binding sites on bovine serum albumin. A 19F-NMR study, Dubois et al, *Proc. Natl Acad Sci* 90:6478-6487, 1993.
30. Clinical characteristics and biotransformation of Sevoflurane in healthy human volunteers. D.A. Holaday and F.R. Smith, *Anesthesiology* 54:100-106, 1981.
31. Uptake, elimination and biotransformation of volatile anesthetics in humans: A comparative study of Sevoflurane with Halothane, Enflurane, and Isoflurane. Y. Shiraishi and K. Ikeda, Hamamatsu University, unpublished report, October 1986.
32. Comparison of the kinetics of Sevoflurane and Isoflurane in humans. Yasuda et al, *Anesthesia and Analgesia* 72:316-324, 1991.
33. Plasma inorganic fluoride with Sevoflurane anesthesia: Correlation with indices of hepatic and renal function. Frink et al, *Anesthesia and Analgesia* 74:231-235, 1992.
34. Serum and urinary inorganic fluoride concentrations after prolonged inhalation of Sevoflurane in human. Kobayshi et al, *Anesthesia and Analgesia* 74:753-757, 1992.
35. Phase I clinical study- identification of the urinary metabolite of Sevoflurane in man by GC-MS. Imai et al, Maruishi Pharmaceutical Co., Ltd. report, August 1986.
36. Urinary excretion of hexafluoroisopropanol glucuronide and fluoride in patients after

- Sevoflurane anesthesia. Gazing et al, *Journal of Pharmacy and Pharmacology* 45:67-69, 1993.
37. Identification of cytochrome P450 2E1 as a predominant enzyme catalyzing human liver microsomal defluorination of Sevoflurane, Isoflurane, and Methoxyflurane. Kharasch et al, *Anesthesiology* 79:795-807, 1993.
  38. Partition coefficients for Sevoflurane in human blood, saline, and olive oil. D.P. Sturm and E.I. Eger II, *Anesthesia and Analgesia* 66:654-656, 1987.
  39. Solubility of I-653, Sevoflurane, Isoflurane and Halothane in human tissue. Yasuda et al, *Anesthesia and Analgesia* 69:370-3, 1989.
  40. Synthesis of fluoro-dideuteromethyl 1,1,1,3,3,3-hexafluoro-2-propyl ether (deuterated Sevoflurane). Baker et al, *J Labelled Compounds and Radiopharmaceuticals* 33:801-807, 1993.

### Toxicology Studies

#### A. Acute Inhalation Toxicity Studies:

1. Acute toxicity studies in four species (IND)
2. Inhalational acute toxicity study of Sevoflurane in mice. M. Tamada, Central Research Laboratories, Maruishi Pharmaceutical Co., Ltd. Study SEVO-4A27;(1985).
3. An acute toxicity study of Sevoflurane in neonatal mice. M. Tamada, Central Research Laboratories, Maruishi Pharmaceutical Co., Ltd. Study SEVO-5A27;(1986).
4. Inhalational acute toxicity study of Sevoflurane in rats. M. Tamada, Central Research Laboratories, Maruishi Pharmaceutical Co., Ltd. Study SEVO-4A37;(1985).
5. Acute toxicity of Sevoflurane in neonatal rats at seven days of age by inhalational administration. Y. Kawai, Central Research Laboratory, Maruishi Pharmaceutical Co., Ltd. (1990)
6. An acute inhalation study of Sevoflurane in cynomolgus monkeys. Inc. Report 84-2815;(1985).

#### B. Acute Oral Toxicity Studies:

1. Acute toxicity study of Sevoflurane administered orally in mice. M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Ltd., Study SEVO-6A21;(1986).
2. Acute toxicity study of Sevoflurane administered orally in rats. M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-6A31;(1986).

#### C. Acute Intraperitoneal Toxicity Studies:

1. Acute toxicity study of Sevoflurane administered intraperitoneally in mice. M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-6A24;(1986).
2. Acute toxicity study of Sevoflurane administered intraperitoneally in rats. M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-6A34;(1986).

### Subchronic Repeated Dose Studies

1. Eight week inhalational subacute toxicity study of Sevoflurane in rats. M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-4S37;(1987).
2. Two week subacute toxicity study in dogs. (IND)

3. Subacute inhalation studies of Sevoflurane and Halothane in *Macaca fascicularis*.  
ND
4. An eight week inhalation toxicity study of Sevoflurane in cynomolgus monkeys. W. Tierney,  
Report 84-2866;(1985).

#### Developmental and Reproductive Toxicity Studies

##### Inhalation Studies:

1. Toxicity study of Sevoflurane given prior to and in the early stages of pregnancy in rats. M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-4R3A;(1986).
2. Toxicity study of Sevoflurane given during the period of fetal organogenesis in rats. M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-5R3B;(1986).
3. Teratogenicity study of Sevoflurane, an inhalational anesthetic, in rabbits (segment II test). H. Katayama, 1986).
4. Toxicity study of Sevoflurane given during the perinatal and lactation period in rats. M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-5R3c;(1986).

#### Mutagenicity studies

1. Mutagenicity study of Sevoflurane by use of microorganisms (Ames test). M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-5M1A;(1985).
2. Bacterial reverse mutation assay (Ames test plus *E. coli*) of Sevoflurane. M. Diehl, Drug Safety Evaluation Division, Abbott laboratories, TX93-076; R&D/93/450, (1993).
3. Micronucleus test with mice of Sevoflurane. Y. Kawai, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-2M27; (1993)
4. Chromosomal aberration test of Sevoflurane with mammalian cells in culture. T. Mizuno, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-5M1B; (1986)
5. Sevoflurane L5178YTK +/- mouse lymphoma mutagenicity assay. C. Bigger and J. Clarke, Microbiological Associates, Abbott Laboratories, TX93-210; R&D/93/725, (1993).
6. In vitro cytogenetics human lymphocyte culture assay of Sevoflurane. M. Diehl, Drug Safety Evaluation Division, Abbott laboratories, TX93-075; R&D/93/400, (1993).
7. Mammalian cell transformation assay (Balb/c-3T3). D. Putnam, Abbott Laboratories, TX93-211; R&D/93/876, (1993).
8. Sevoflurane <sup>32</sup>P post-labeling DNA adduct assay in mouse liver.  
Abbott Laboratories, R&D R&D/93/879, (1993).

#### Special Toxicity Studies

##### Immunotoxicity:

1. Acute systemic anaphylaxis of Sevoflurane in guinea pigs. M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-5T47; (1985).

##### Hepatotoxicity Studies:

1. Evaluation of hepatotoxic potential of Sevoflurane in rats. L. Martis, Inc.,

Project No. CCS108A, Protocol 38-7, (1980).

2. Evaluation of hepatotoxic potential of Sevoflurane in guinea pigs, (1974).
3. The effect on the liver of beagles by single inhalation of Sevoflurane. (1989).
4. Glucose study in dogs. E. Woods 1978 (IND)

#### Irritation Studies

1. Eye irritation study in rabbits. (IND)
2. Eye irritation test of Sevoflurane. M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-4T5A; (1985)

#### Toxicity and Mutagenicity Studies of Hexafluoroisopropanol (HFIP)

##### A. Inhalation Studies:

1. An acute toxicity of hexafluoroisopropanol (HFIP) in rats by inhalational administration. M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Study HFIP-6A37; (1987).

##### B. Intraperitoneal Studies:

1. An acute toxicity of hexafluoroisopropanol (HFIP) in rats by intraperitoneal administration. M. Tamada, Maruishi Pharmaceutical Co., Study HFIP-6A34; (1987).

##### C. Intravenous Studies:

1. An acute toxicity of HFIP in rats by intravenous administration. Laboratory, Maruishi Pharmaceutical Co., Study HFIP-8A33; (1988c).
2. Seven days intravenous toxicity study of HFIP in rats. Maruishi Pharmaceutical Co., Study HFIP-8T3A; (1988d).

##### D. Mutagenicity Studies:

1. A mutagenicity study of hexafluoroisopropanol by use of microorganisms (Ames test). T. Mizuno, Central Research Laboratory, Maruishi Pharmaceutical Co., Study HFIP-7M1A; (1988a).

#### Toxicity Studies of Compound A:

##### Inhalation Studies:

1. Acute toxicity of compound A in rats by one hour inhalational administration. Central Research

- Laboratory, Maruishi Pharmaceutical Co., Ltd., Study CA-7A37; (1987).
2. Acute ( 3 hour) inhalation toxicity study of compound A/Sevoflurane in the rat. G. Hoffman and W. Wooding, Pharmacu LSR, Inc., Abbott Laboratories, TA93-423 (1994)
  3. Acute toxicity of compound A in rats by three hours inhalational administration. Y. Kawai, Central Research Laboratory, Maruishi Pharmaceutical Co., Ltd., Study CA-8A37; (1988 a).
  4. Toxicity of compound A in rats: Effect of a 3-hour administration. Gonsowski et al, Anesthesiology 1994; 80:556-65.
  5. Toxicity of compound A in rats: Effect of increasing duration of administration. Gonsowski et al, Anesthesiology 1994; 80:566-573.
  6. Subacute toxicity of compound A on 28 alternate days in rats by inhalation. Y. Kawai, Central Research Laboratory, Maruishi Pharmaceutical Co., Ltd., Study CA-8S37; (1989).

#### Mutagenicity Studies:

1. Ames metabolic activation test to assess the potential mutagenic effect of I-654 (1986).
2. Chromosome aberration test of compound A with mammalian cells in culture. T. Mizuno, Central Research Laboratory, Maruishi Pharmaceutical Co., Ltd., Study CA-7M1A; (1988b).

#### Special Toxicity Studies:

1. Evaluation of compound A for active systemic anaphylaxis in guinea pigs. K.R. Hahn, Drug Safety Evaluation Division, Abbott Laboratories, TF83-418; R&D/93/748, (1993).

#### Toxicity Studies of Compound B

##### Acute Inhalational Study:

1. Acute toxicity of compound B in rats by three hours inhalational administration. Y. Kawai, Central Research Laboratory, Maruishi Pharmaceutical Co., Ltd., Study CB-8A37; (1988b).

##### Mutagenicity Study:

1. A mutagenicity study of compound B by use of microorganisms (Ames test). T. Mizuno, Central Research Laboratory, Maruishi Pharmaceutical Co., Ltd., Study CB-8M1A; (1988c).

Note - Portions of the following review were excerpted directly from the sponsor's submission. Studies reviewed previously are summarized in the evaluation sections.

#### Abbreviations used in these studies:

\* =  $p \leq 0.05$  \*\* =  $p \leq 0.01$  \*\*\* =  $p \leq 0.001$   
 ppm = parts/million G = group(s) D = day(s)  
 LC<sub>50</sub> = 50% lethal concentration

## (i) Pharmacology

Pharmacology Studies:

## A. Neuropharmacological Studies:

1. The effect of Sevoflurane on central blood flow, cerebral metabolic rate for oxygen, intracranial pressure, and the electroencephalogram are similar to those of Isoflurane in rabbit. Scheller et al, Anesthesiology 1988; 68:548-51. The data suggested that the effects of sevoflurane at 0.5 and 1.0 MAC on CBF, CMRO<sub>2</sub>, and EEG are indistinguishable from those of equivalent concentrations of isoflurane in the rabbit.

2. Effects of Sevoflurane on the intracranial pressure in dogs. Anesthesiology, The ICP was increased dose-dependently in dogs with sevoflurane inhalation (1 and 2 MAC) for the short duration (30 min.). However, the increase was not as great as that with halothane.

3. Effects of Sevoflurane on electroencephalographic activity in rats-compared with Enflurane and Halothane. Department of Pharmacology, Faculty of Medicine Sevoflurane and enflurane produced similar pattern of EEG changes. After inhalation, EEG changes returned to baseline rapidly.

4. The effect of Sevoflurane on somatically induced sympathetic reflexes. Yanase et al, J Anesth 1988;2:272-5. The sympathetic A- (myelinated) and C-reflexes (unmyelinated) were depressed in parallel by sevoflurane administration in a dose dependent manner (2%, 3% and 4%) in six cats.

5. Effect of Sevoflurane on central nervous system. Anesthesiology, Sevoflurane caused EEG changes very close to those caused by enflurane. Sevoflurane, like enflurane, at higher concentrations could induce spikes and seizures due to somatic or photic stimulation where spontaneous spike appeared. Since the MAC of sevoflurane is reported to be 2.36% in dogs, more or less the same MAC may be expected in cats. Therefore, the spasmogenic concentration is considered to be much higher than the clinical concentration.

6. The effect of Sevoflurane, a new inhalational anesthetic, on spinal reflex action potentials. Central Research Laboratory, Maruishi Pharmaceutical Co., Ltd. Both sevoflurane and enflurane did not significantly affected monosynaptic reflex potential when administered in concentrations ranging from a subanesthetic dose (2%) to a supra-anesthetic dose (5%) in cats. Neither sevoflurane nor enflurane exerted any marked influence on the descending inhibitory and excitatory systems from the brain to the spinal cord.

7. Central effects of the new inhalation anesthetic Sevoflurane - effects on EEG arousal and recruiting responses and hippocampal after-discharge. Central Research Laboratory, Maruishi Pharmaceutical Co., Ltd. Sevoflurane

selectively inhibited the ascending reticular activating system which project on the cerebral cortex. Sevoflurane has no remarkable effect on the nucleus centrum medianum of the thalamus-cortical system.

8. Clinical and experimental studies on the potentiation of neuromuscular blocking effects of vecuronium and pancuronium by Sevoflurane. Itagaki et al. Sevoflurane at 1 MAC did not block the transmission of neuromuscular impulses and produced a greater vecuronium-potentiating effect than halothane. This may be due to sevoflurane effect on the nerve fascia including the end-plate.

9. General pharmacological study of HFIP - observation of the effects of HFIP on the central nervous system and general condition. Bakoshi et al, Central Research Laboratory, Maruishi Pharmaceutical Co., Ltd. Intravenous administration of hexafluoroisopropanol (HFIP), a metabolite of sevoflurane, at 26.6 mg/kg did not effect the nervous system and general condition of ICR male mice. HFIP at 53.2 mg/kg produced inhibition of spontaneous motor activity during 0-15 minutes after administration. In the 75.2 mg/kg group (LD<sub>50</sub> value - 106.4 mg/kg), one animal died immediately and 2 showed a loss of righting reflex at 3 minutes post administration. All animals in this group showed decreases in motor activity, muscle tone, awareness, and grip strength and difficulty in body holding.

10. General pharmacological study of HFIP - effect of HFIP on spontaneous motor activity in mice. Bakoshi et al, Central Research Laboratory, Maruishi Pharmaceutical Co., Ltd. HFIP inhibited the degree and duration of spontaneous motor activity in a dose-dependent manner (26.6, 53.2 and 75.2 mg/kg) in male ICR mice. Unlike induction, recovery was not concentration-dependent.

#### B. Cardiovascular/Respiratory Studies

1. Comparison of the epinephrine-induced arrhythmogenic effect of Sevoflurane with Isoflurane and Halothane. S. Imamura and K. Ikeda, J Anesth 1987;1:62-8. The mean values of the arrhythmogenic infusion rates of epinephrine and the corresponding levels in mongrel dogs were 17.3 ug/kg/min and 275.7 ng/ml for sevoflurane, 6.7 ug/kg/min and 149.2 ng/ml for isoflurane, and 1.9 ug/kg/min and 39.1 ng/ml for halothane, respectively. The data indicate that sevoflurane may be better than halothane when epinephrine is used during anesthesia.

2. Cardiovascular interaction between Sevoflurane and nicardipine in open chest dogs. Iwatsuki et al, J Anesthesia 1988;2:146-53. The bolus intravenous injection of nicardipine, a calcium channel blocker, at doses of 15 ug/kg and 30 ug/kg under sevoflurane anesthesia produced transient decreases in blood pressure, systemic vascular resistance, left ventricular pressure, left ventricular dp/dt and -dp/dt, and a slight increase in cardiac output. The degrees of these changes were almost similar to those under thiopental or halothane anesthesia.

3. Arrhythmogenic threshold of epinephrine during Sevoflurane, Enflurane and Isoflurane anesthesia in dogs. Hayashi et al, Anesthesiology 1988;69: 145-7. The arrhythmogenic plasma levels of epinephrine was highest during isoflurane anesthesia, lowest during enflurane anesthesia, and intermediate for sevoflurane.

4. The comparative cardiovascular effects of Sevoflurane with Halothane and Isoflurane. Kazama et al, J Anesth 1988;2:63-8. The suppression of left cardiac function by sevoflurane was greater in close chest mongrel dogs than that of isoflurane, and less than that of halothane. Heart rate and systemic vascular resistance with sevoflurane were slightly lower than that of isoflurane. The coronary sinus blood flows with sevoflurane and isoflurane at 1.0 and 2.0 MAC were higher than halothane.

5. Effect of inhalation anesthetic Sevoflurane on atrioventricular conduction in dogs.

The mean arterial pressure and heart rate fell significantly from the control level with an increasing concentration of sevoflurane. The A-H interval showed no significant difference from the control at 0.5 or 1.0 MAC but was slightly prolonged at 1.5 MAC.

6. The effect of Sevoflurane on regional myocardial blood flow in ischemic heart.

The regional myocardial blood flow was decreased dose-dependently in both the ischemic and normal regions in dogs after sevoflurane administration. The I/O ratio was unchanged in the ischemic region but increased in the normal region with increasing concentration of sevoflurane to 2.4% and 3.6%.

7. Influence on hemorrhagic hypotension under Sevoflurane and Halothane anesthesia on renal circulation and metabolism.

No statistically significant differences in the effect on renal circulation and metabolism in mongrel dogs were observed between halothane and sevoflurane treatment groups.

8. Effects of Halothane, Isoflurane, Sevoflurane and Enflurane on portal venous pressure in the isolated perfused rat liver.

Halothane increased portal venous pressure in isolated perfused rat liver by  $164.5 \pm 31.0\%$ , unlike isoflurane and sevoflurane reduced by  $41.3 \pm 6.8$  and  $26.8 \pm 3.7\%$ , respectively. Enflurane exposure resulted in a small reduction in PVP which did not differ statistically from control.

9. Effects of Sevoflurane and Isoflurane on cardiac and coronary dynamics in chronically instrumented dogs. Bernard et al, Anesthesiology 1990;72:659-62. Sevoflurane and isoflurane produced similar effects (aortic hypotension, systemic vasodilation, decrease in stroke volume and decrease in left ventricular dP/dt) except for heart rate. At 1.2 MAC, sevoflurane produced a greater increase in heart rate than isoflurane ( $+60 \pm 12\%$  vs  $33 \pm 9\%$ ).

10. Sevoflurane anesthesia: compatibility with morphine, atropine, succinylcholine, lidocaine and pentothal. Study performed

Administration of morphine, atropine, succinylcholine, lidocaine and pentothal prior to or during sevoflurane administration anesthesia did not cause unusual effects on arterial blood pressure, respiration or pulse rates in dogs.

11. Synthetic organic chemicals (comparison of arrhythmogenic effects evoked by various pressoramines under Halothane or Sevoflurane anesthesia in dogs. Originally submitted under IND on May 15, 1969. Sevoflurane was less sensitizing to the



20. Comparison of MAC and the rate of rise of alveolar concentration of Sevoflurane with Halothane and isoflurane in the dog. T. Kazama and K. Ikeda, *Anesthesiology* 1988;58:435-437. The minimum alveolar concentrations of sevoflurane, isoflurane and halothane were  $2.36 \pm 0.46$  (n=18),  $1.39 \pm 0.25$  (n=10), and  $0.89 \pm 0.20$  (n=12), respectively, in mongrel dogs.

21. The minimum alveolar concentration of Sevoflurane in cats. Doi et al, *J Anesthesia* 1988;2:113-114. MAC values for human, cat and dog are given below.

	Human	Cat	Dog
Sevoflurane	1.71	$2.58 \pm 0.3$	$2.36 \pm 0.46$
Halothane	0.77	$1.19 \pm 0.15$	$0.87 \pm 0.04$
Enflurane	1.68	$2.37 \pm 0.16$	$2.06 \pm 0.13$
Isoflurane	1.15	$1.61 \pm 0.10$	$1.28 \pm 0.25$
Sevoflurane/ Halothane	2.22	2.19	2.71
Sevoflurane/ Enflurane	1.02	1.09	1.14
Sevoflurane/ Isoflurane	1.49	1.6	1.84

The value for sevoflurane in the cat is from this study.

22. MAC of Sevoflurane in humans and the New Zealand white rabbit. Scheller et al, *Can J Anesth* 1988;35:153-6. The MAC of sevoflurane in the rabbit was  $3.7 \pm 0.16\%$ . MAC ratios of various volatile anesthetic pairs in the human (this study), rabbit (this study) and human (Kato et al., *Anesthesiology* 1987;66:301-303) are given below.

MAC ratio	Sevoflurane Isoflurane	Sevoflurane Halothane	Sevoflurane Enflurane
Human (this study)	1.78	2.69	1.22
Rabbit	1.8	2.6	1.29
Human (Kato et al)	1.48	2.25	1.02

The possible explanation for the discrepancy between these two data may be due to differences in the methodology used and/or population studied.

23. The minimum alveolar concentration (MAC) and hemodynamic effects of Halothane, Isoflurane and Sevoflurane in newborn swine.

The MAC values for halothane, isoflurane and sevoflurane were  $0.90 \pm 0.12$ ,  $1.48 \pm 0.21$  and  $2.12 \pm 0.39$ , respectively. Awake hemodynamic parameters did not differ among the three anesthetic groups.

#### C. Genitourinary Studies:

1. Effect of Sevoflurane on isolated rat uterus and vas deferens. Bakoshi et al, Central Research Laboratory, Maruishi Pharmaceutical Co., Ltd. A linear relationship (from 0.5 to 8%) was found between bubbling concentration and dissolved concentration of enflurane, halothane and sevoflurane. The inhibitory action on the contraction of spontaneous movement of estrous and pregnant uterus was weakest for sevoflurane, followed by enflurane and halothane. The relative strengths of the inhibitory action on the contraction of segments of epinephrine-induced contracted vas deferens were halothane > enflurane > sevoflurane.

#### D. Miscellaneous Physiological Studies:

1. General pharmacological studies of Sevoflurane. Makoshi et al, Central Research Laboratory, Maruishi Pharmaceutical Co., Ltd. Sevoflurane showed inhibitory activity against convulsions and analgesic effect on pain or deep pain sensation due to tail pinching. The effective concentration of sevoflurane for muscle relaxation was higher than enflurane or halothane. Sevoflurane caused less decrease in blood pressure and body temperature during anesthesia as compared with the control drugs. Sevoflurane has some direct effects on cardiac function and gastrointestinal system.

2. Variations in onset of porcine malignant hyperthermia. G.A. Gronert and J.H. Milde, Anesth Analg 1981;60:499-503. Poland China swine were susceptible to malignant hyperthermia after exposure to sevoflurane or halothane.

3. Malignant hyperthermia induction in susceptible swine following exposure to Sevoflurane. C.H. Sevoflurane caused weak malignant hyperthermia (MH) in Poland China swine. Several hours of sevoflurane exposure were required to trigger the MH syndrome.

4. Sevoflurane effect on control pigs and Halothane comparative effect in triggering malignant hyperthermia in MHS pig #15, 9, 17.

Halothane was more potent triggering agent for malignant hyperthermia than sevoflurane as evidenced by the shorter time required to trigger MH in Poland China swine

5. Study on the hemolytic effect of Sevoflurane using human and rabbit erythrocytes. Yoshimura et al, Central Research Laboratory, Maruishi Pharmaceutical Co., Ltd. Sevoflurane showed no hemolytic effect at 75, 150 and 300 ug/ml in human and rabbit blood.

6. Hepatic effects of Sevoflurane - the changes of drug metabolizing enzymes and morphic features  
Cytochrome P450 was

increased in all exposed Wistar rats compared to control animals. The hepatic GOT and GPT were either unchanged or reduced by the anesthetic.

7. Thermoregulatory defect in rats during anesthesia. Hitt et al, *Anesthesia Analgesia Curr Res* 1977;56:388-94. Phenobarbital (1 mg/ml in drinking water) treatment in combination with sevoflurane (0.5%, 1.4%), enflurane (0.4%) or methoxyflurane (0.07%) resulted in a loss of thermoregulatory ability in rats (Fisher 344, Sprague-Dawley, Brattleboro, Wistar) resulting in lethal hyperthermia. Harley guinea pigs and Balb/C mice were unaffected. Rats drinking ordinary tap water and phenobarbital-treated rats not exposed to either soda lime or exogenous heat were not affected by anesthetics.

#### Summary and Evaluation of Pharmacology

Sevoflurane is fast acting and is associated with rapid changes in anesthetic depth and rapid arousal. Scheller et al (*Anesthesiology* 1988;68:548-51) had demonstrated that the effect of Sevoflurane on central blood flow, cerebral metabolic rate for oxygen, intracranial pressure, and the electroencephalogram were similar to those of Isoflurane in rabbit.

Sevoflurane appears to have a general suppressive effect on sympathetic A- and C-reflexes, rather than C-reflex more than A-reflex reported for morphine and fentanyl. Unlike halothane, sevoflurane and enflurane do not appear to have muscle relaxant activity at the spinal level in cats.

Intravenous administration of hexafluoroisopropanol (HFIP), a metabolite of sevoflurane, at 75.2 mg/kg (~70% of the LD<sub>50</sub>) produced neurological changes including decreases in motor activity and muscle tone in ICR male mice.

Mean MAC of sevoflurane for the various species were as follow:

Species	MAC (%)
Mice	2.3
Rats	2.2
Rabbits	1.97, 3.61, 3.7
Dogs	2.36
cats	2.58
Swine (newborn)	2.12
Human - Neonates	3.3
Infants	2.6 - 3.0
Children	2.5 - 2.7
Adults	2.0 - 2.6
Elder (70 - 87 Y)	1.44

It is generally recognized that an inhalational anesthetic agent which does not sensitize the myocardium to epinephrine has clinical advantages. Imamura and Ikeda (J Anesth 1:62-68) in 1987 demonstrated that the arrhythmogenic doses of epinephrine in dogs during sevoflurane and isoflurane anesthesia were significantly higher than those during halothane anesthesia. This indicates that sevoflurane did not stimulate the sensitivity of the myocardium to epinephrine as much halothane did. Sevoflurane may be better than halothane.

Cardiovascular interaction of nicardipine, a calcium channel blocker, and sevoflurane was additive in dogs similar to that of nicardipine and halothane. The effects of sevoflurane on cardiac function and coronary blood flow were identical to those induced by isoflurane in the chronically instrumented dog except that 1.2 MAC sevoflurane produced a greater increase in heart rate than 1.2 MAC isoflurane..

Sevoflurane reduced diastolic coronary vascular resistance in chronically instrumented dog with intact autonomic nervous system (ANS) reflexes indicating that sevoflurane may possess coronary vasodilating properties. Sevoflurane also depressed myocardial contractility, prolonged isovolumic relaxation, and decreased rapid ventricular filling without affecting regional chamber stiffness in ANS intact and blocked dogs suggesting that the left ventricular systolic and diastolic mechanical consequences of sevoflurane occur independent of ANS activity. Sevoflurane did not reduce collateral myocardial perfusion or cause coronary steal in chronically instrumented canine model of multivessel coronary disease.

The rise of alveolar concentration toward that of the inspired concentration ( $F_a/F_i$ ) was significantly faster in mongrel dogs for sevoflurane than that for halothane or isoflurane. The inhibitory effect of both sevoflurane and enflurane against spontaneous movement and oxytocin-induced contractions of estrous and pregnant uterus was about the same when  $IC_{10}$  and  $IC_{50}$  values were expressed by dissolved concentration.

Both halothane and isoflurane depressed the hemodynamics in new born swine more than sevoflurane at equipotent concentrations. Sevoflurane triggered slow and reversible malignant hyperthermia in susceptible pigs (Poland China swine) as compared to halothane..

The hepatic metabolizing enzyme, cytochrome P450, was induced in Wistar rats exposed to sevoflurane without any cytological or biochemical evidence of hepatotoxicity.

### (II). Pharmacokinetics

#### Drug Metabolism

1. The blood concentration of Sevoflurane after inhalation in rats. Tamada et al, Maruishi Pharmaceutical Co., Ltd. Report, November 1986; P 2658/V 7. Sevoflurane [Lot No. 6x08] was administered to Wistar SPF rats ( 5 animals/sex/group, 8 weeks old, 134-222 g body weight) by inhalation in pure oxygen at a concentration of 2.3%. The flow rate was set 2 L/min, the respiratory rate at 50 per minute, and the respiration time 0.4 second. Seven groups were used for the determination of blood concentration at 1, 3, 5, 10, 20, 30, and 60 minutes after initiation of inhalation and five groups for the determination of blood concentration after 30-minutes Sevoflurane inhalation and subsequent 3, 5, 10, 20, and 30 minutes of pure oxygen inhalation.

Mean Sevoflurane blood concentrations in male and female rats during and after inhalation

are given below:

Mean Sevoflurane blood concentration (Micrograms Per Milliliter)						
Minutes	Males			Females		
	Mean	±	SD	Mean	±	SD
<b>During Sevoflurane Inhalation</b>						
1	142.6	±	9.2*	141.2	±	15.1*
3	158.4	±	9.1	163.9	±	8.9
5	161.1	±	10.2	168.5	±	4.0*
10	162.1	±	18.2	199.2	±	24.8
20	175.6	±	8.4	204.8	±	15.4
30	174.4	±	22.1	216.0	±	6.0*
60	208.6	±	23.0	249.1	±	27.3

After Stopping Sevoflurane Inhalation						
3	14.5	±	2.2*	18.3	±	1.4*
5	10.6	±	0.9*	10.7	±	2.6
10	8.9	±	2.2	7.0	±	1.1*
20	5.0	±	0.9**	4.9	±	0.7*
30	3.3	±	0.8*	3.4	±	0.9

Legend:

n = 5, except \* where n = 4 and \*\* where n = 3

The biological half-life was estimated to be 14.4 minutes in males and about 19.2 minutes in females.

2. Time course of free HFIP and HFIP glucuronide concentrations in blood after intravenous administration of HFIP to rats. Yoshimura et al, Maruishi Pharmaceutical Co., Ltd. Report, August 1988; P 3406/V 9. Hexafluoroisopropanol (HFIP), a major metabolite of sevoflurane, was administered into the caudal vein of 5 week old SD rats and the plasma concentration of free HFIP and HFIP glucuronide were determined at intervals as shown below.

Free HFIP:HFIP Glucuronide in plasma of rats after intravenous administration of HFIP

Minutes	60 mg/kg	40 mg/kg
15	29:71	25:75
30	12:88	10:90
90	0:100	0:100

Free HFIP was rapidly converted to glucuronide conjugate and by 90 minutes free HFIP could not be

detected.

3. Elimination kinetics of Sevoflurane and Halothane from blood, brain and adipose tissue in the rat. Stern et al, *Anesthesia and Analgesia* 1990; 71:658-664; P 2289/V 6. Male S-D rats, weighing 250-300 g, were anesthetized with sevoflurane (3% in oxygen) or halothane (1.5% in oxygen) for 1 hour. The concentrations used were 1.3 times the MAC for each agent.

The rapid,  $\alpha$ -elimination rates of sevoflurane from blood and brain were faster than the corresponding rates for halothane. The slower,  $\beta$ -elimination rates from brain, blood and adipose tissue were similar for both volatile anesthetics as shown below.

		$\alpha$ -elimination (min)	$\beta$ -Elimination (min)
Blood	Sevoflurane	0.58 $\pm$ 0.03	26 $\pm$ 5.0
	Halothane	1.29 $\pm$ 0.15	36 $\pm$ 5.6
Brain	Sevoflurane	1.60 $\pm$ 0.10	34 $\pm$ 11
	Halothane	2.70 $\pm$ 0.66	34 $\pm$ 7.8
Adipose	Sevoflurane	-	241 $\pm$ 53
	Halothane	-	246 $\pm$ 51

Anesthetic Elimination Time Constants

4. General anesthetic distribution in rat brain;  $^{19}\text{F}$ -MRI of Sevoflurane. Xu et al, *Anesthesiology* 79:A414, 1993; ASA Abstract; P 3340/V 9. Adult male S-D rats were anesthetized by sevoflurane and three-dimensional Fourier transformation  $^{19}\text{F}$ -magnetic resonance imaging was used to follow the distribution of sevoflurane in the brain. Comparison of  $^{19}\text{F}$  images showed heterogenous distribution of the anesthetic in brain.

5. Ionchromatographical analysis of a glucuronide as a Sevoflurane metabolite. Fujii et al, *Hiroshima J Anesthesia* 23:3-7, 1987; P 396/V 2. The glucuronide of hexafluoroisopropanol was detected in the bile of sevoflurane treated rats. The concentration of this substance in the rat bile increased linearly during inhalation and depend on the inhaled sevoflurane concentration.

6. Excretion of a glucuronide in bile as a Sevoflurane metabolite during Sevoflurane anesthesia. Fujii et al, Department of Anesthesiology, Hiroshima University School of Medicine, unpublished report, August 1985; P 387/V 2. Wistar rats of 100-150 g in body weight, surgically prepared to tracheostomy and cannulation of the common bile duct, were exposed to sevoflurane (1.0 or 2.0%) in oxygen for 4 hours and then ventilated with pure oxygen.

The concentration of the substance detected in the bile increased in time and concentration dependent manner. This increase in the metabolite was not effected by phenobarbital pretreatment of the animals. Methylcholanthrene pretreatment of the animals decreased the concentration of this metabolite in the bile.

7. Deuteration reduced significantly the biotransformation of Sevoflurane. D.A. Holaday and R. England, *Anesthesiology* 57:A246, 1982; ASA Abstract; P 634/V 3. Male Sprague-Dawley rats (200-250 g body weight) were treated with saline (0.25 ml, i.p. for 7 days), phenobarbital (0.2 g/100 ml in drinking water for 6 days) or isoniazid (0.5 mg/kg/day, i.p. for 7 days). Then sevoflurane or deuterated sevoflurane substituted with deuterium for the hydrogen atoms (10 mmole/kg, i.p. in Tween 80) was given.

Total and inorganic fluoride concentrations in the plasma, tissue and urine were determined. Urinary excretion of fluoride ion ( $\mu\text{g}/48$  hours) in rats is given below.

	Saline	Phenobarbital	Isoniazid
Pre-exposure	116 $\pm$ 6.3	85.8 $\pm$ 3.9	106 $\pm$ 4.2
Sevoflurane	200 $\pm$ 22.3	367 $\pm$ 55.2	297 $\pm$ 36.7
Deuterated Sevoflurane	123 $\pm$ 8.1*	131 $\pm$ 12.3**	165 $\pm$ 12.5*

Legend: Significantly different from sevoflurane (nondeuterated) group; \* $p < 0.02$ ; \*\* $p < 0.001$

8. Inhibitory effects of deuterium substitution on the metabolism of Sevoflurane by the rat. Baker et al, *Drug Metabolism and Disposition* 21:1170-1171, 1993; P 53/V 2. *In Vitro Exposures.* Male Sprague-Dawley rats (180-200 g) were treated with isoniazid (50 mg/kg/day, ip) or sodium phenobarbital (0.2% in drinking water) for four days before being sacrificed. Hepatic microsomes of untreated and treated rats were incubated in sealed plastic vials under sevoflurane headspace concentration of 0.5% for 30 min at 37°C.

*In Vivo Exposures.* Rats (untreated, isoniazid or phenobarbital-treated) were exposed to either no anesthetic, sevoflurane or deuterated sevoflurane (3%, v/v) in a 3.8 liter plastic chamber containing 250 g soda lime under a wire mesh floor. After 30 minutes of exposure the chamber was flushed with oxygen for 5 min. Blood samples were collected within 15 minutes of sevoflurane exposure.

**Assays.** Fluoride was measured with ion-specific electrodes.

**Results.** Fluoride release from sevoflurane and deuterated sevoflurane metabolism in hepatic microsomes from untreated, isoniazid-treated, or phenobarbital-treated rats is given below.

Treatment	Nmol fluoride/mg Microsomal Protein	
	Sevoflurane	Deuterated Sevoflurane
None	1.36 $\pm$ 0.05	0.08 $\pm$ 0.02
Phenobarbital	0.93 $\pm$ 0.10	0.08 $\pm$ 0.04
Isoniazid	5.14 $\pm$ 0.38	0.90 $\pm$ 0.06

The metabolism of sevoflurane was ~4-times higher following isoniazid pretreatment whereas phenobarbital pretreatment did not increase the biotransformation of sevoflurane. The metabolism of

deuterated sevoflurane was substantially inhibited compared to sevoflurane.

Plasma fluoride levels in untreated, isoniazid-treated, or phenobarbital-treated rats after exposure to sevoflurane or deuterated sevoflurane are shown below.

Treatment	$\mu\text{M Fluoride} \pm \text{SE}$		
	No Exposure	Sevoflurane	Deuterated Sevoflurane
None	0.6 $\pm$ 0.2	8.4 $\pm$ 0.7	5.4 $\pm$ 0.5
Isoniazid	0.9 $\pm$ 0.1	16.6 $\pm$ 1.5	6.2 $\pm$ 0.5*
Phenobarbital	1.6 $\pm$ 0.2	19.0 $\pm$ 2.4	7.4 $\pm$ 0.8*

\* Significant difference from the corresponding sevoflurane values.

The fluoride concentrations in the rats exposed to the deuterated compound were 38% lower in the control group, 66% lower in the isoniazid group, and 67% lower in the phenobarbital group. Treatment with either phenobarbital or isoniazid resulted in about 2-fold higher fluoride concentrations after exposure to sevoflurane but not to deuterated sevoflurane.

9. Metabolism of Synthane: Comparison with in vivo and in vitro defluorination of other halogenated hydrocarbon anesthetics. Mazze et al, Br J Anaesthesiology 51:839-844, 1979; P 1498/V 5. Microsomes prepared from treated and untreated adult male Fischer 344 rats were incubated in the presence of various anesthetics and results are compared below.

Metabolism of anesthetics by male Fisher 344 rats			
Substrate	nmole F/mg protein/30 minutes		
	Control	Phenobarbital Induced	Induced/control
Sevoflurane	1.82 $\pm$ 0.30	3.22 $\pm$ 0.46	1.90 $\pm$ 0.25
Methoxyflurane	2.0 $\pm$ 0.11	18.89 $\pm$ 2.40	9.75 $\pm$ 1.50
Enflurane	1.31 $\pm$ 0.23	1.63 $\pm$ 0.15	1.35 $\pm$ 0.15
Isoflurane	0.51 $\pm$ 0.09	1.51 $\pm$ 0.25	3.6 $\pm$ 0.80
Halothane	<0.1	<0.1	-
Synthane	0.1	<0.1	-

Data expressed as mean  $\pm$  SEM

Halothane and synthane were not defluorinated.

10. Effect of phenytoin (DPH) treatment on Methoxyflurane metabolism in rats. Caughey et al, J Pharm Exp Therapeutics 210:180-185, 1979; P 159/V 2. The toxicity and metabolism of fluorinated anesthetic methoxyflurane are compared in Fischer 344 rats in this paper. In vitro studies demonstrated that pretreatment of rats with phenobarbital (1 mg/ml in the drinking water for 5 days) or phenytoin (200 mg/kg, p.o. for 4 days) enhanced the microsomal defluorination of

anesthetics as shown below.

	Control	Phenobarbital	Phenytoin
(nmol F/mg protein/15 min)			
Methoxyflurane	2.5 ± 0.1	32.2 ± 3.5**	32.8 ± 2.0**
Enflurane	1.4 ± 0.2	2.0 ± 0.1	1.7 ± 0.1
Isoflurane	0.7 ± 0.2	1.4 ± 0.2*	1.3 ± 0.1*
Sevoflurane	1.3 ± 0.5	4.1 ± 0.5**	3.9 ± 0.1**

Significantly different from respective control groups; \*p<0.05; \*\*p<0.001

A 10-fold increase in the rate of hepatic microsomal methoxyflurane defluorination were observed after treatment of rats with either phenytoin or phenobarbital. Defluorination of sevoflurane was enhanced by 3-fold by each phenobarbital and phenytoin as compared to untreated animals.

11. Effects of isoniazid treatment on selected hepatic mixed-function oxidases. S.A. Rice and R.E. Talcott, Drug Metabolism and Disposition 7:260-262, 1979; P 1819/V 5. Male Fischer 344 rats (350-450 g, 11-month old) were used in this study. Control rats received i.p. saline. Treated rats received either phenobarbital (0.1% w/v in drinking water for 7 days), isoniazid (50 mg/kg/day, i.p. for 10 days),  $\beta$ -naphthoflavone (80 mg/kg, i.p. in corn oil for 3 days). The hepatic microsomal content of cytochrome P-450 and b5, the defluorination rates of the four volatile ether anesthetics (methoxyflurane, enflurane, isoflurane and sevoflurane; all at 1 mmole/l), and the activities of selected mixed function oxidases are given below.

The defluorination of four volatile ether anesthetics in rats				
nmole F/mg protein/min				
Treatment	<u>Sevoflurane</u>	<u>Methoxyflurane</u>	<u>Enflurane</u>	<u>Isoflurane</u>
Saline	0.14 ± 0.01	0.34 ± 0.02	0.18 ± 0.02	0.08 ± 0.01
Phenobarbital	0.41 ± 0.05*	2.84 ± 0.28*	0.21 ± 0.02	0.16 ± 0.02*
$\beta$ -Naphthoflavone	0.08 ± 0.01*	0.29 ± 0.03	0.08 ± 0.01*	0.07 ± 0.01
Isoniazid	0.56 ± 0.03*	0.82 ± 0.08*	0.77 ± 0.07*	0.27 ± 0.02*

nmole/mg protein/min				
Treatment	Aminopyrine <u>N-Demethylase</u>	<i>p</i> -Nitroanisole <u>O-Demethylase</u>	Ethoxyresorufin <u>O-Deethylase</u>	Aniline <u>Hydroxylase</u>
Saline	1.93 ± 0.19	1.90 ± 0.15	0.24 ± 0.01	0.48 ± 0.03
Phenobarbital	5.33 ± 0.77*	2.83 ± 0.42*	0.26 ± 0.01	1.28 ± 0.18*
$\beta$ -Naphthoflavone	0.99 ± 0.11*	2.92 ± 0.32*	31.0 ± 1.2*	0.37 ± 0.01*
Isoniazid	1.37 ± 0.12*	2.84 ± 0.42*	0.64 ± 0.06*	1.72 ± 0.23*

The defluorination of four volatile ether anesthetics in rats				
Treatment	NADPH Cytochrome c Reductase nmole/mg/min	Cytochrome b <sub>5</sub> nmole/mg	Cytochrome P450 nmole/mg	Cytochrome P450 <sup>+2</sup> + CO $\lambda_{max}$ nm
Saline	238 ± 27	0.62 ± 0.02	1.09 ± 0.03	450
Phenobarbital	453 ± 72*	0.93 ± 0.02*	2.81 ± 0.15*	450
$\beta$ -Naphthoflavone	166 ± 10*	0.55 ± 0.05	1.70 ± 0.12*	448
Isoniazid	234 ± 27	0.66 ± 0.05	1.15 ± 0.08	451

\* Significantly different from control (p < 0.05).

Isoniazid treatment significantly increased the rate of metabolism of p-nitroanisole, ethoxyresorufin, aniline, methoxyflurane, enflurane, isoflurane, and sevoflurane, and significantly decreased the rate of metabolism of aminopyrine. The activities of NADPH-cytochrome c-reductase and the microsomal contents of cytochrome b<sub>5</sub> and p-450 per mg of microsomal protein were not affected.

12. Metabolism by rat hepatic microsomes of fluorinated ether anesthetics following Isoniazid administration. Rice et al, *Anesthesiology* 53:489-493, 1980; P 1814/v 5. Isoniazid (50 mg/kg/day) treatment increased the defluorination rate of Enflurane (370%), Methoxyflurane (259%), Sevoflurane (283%) and Isoflurane (168%) as compared with saline. The hepatic microsomal cytochrome P450 content (expressed as nmol P450/mg protein) was not affected by isoniazid, indicating that one specific form of cytochrome P450 may be effected.

13. Metabolism by rat hepatic microsomes of fluorinated ether anesthetics following ethanol consumption. Rice et al, *Anesthesiology* 58:237-241, 1983. Ethanol treatment enhanced the defluorination rate of Methoxyflurane by 190%, of Enflurane by 298% and of Sevoflurane by 301% as compared to control. There were no differences in body weight, liver weight or hepatic microsomal cytochrome P450 levels between the ethanol treated and their pair-fed controls (sucrose fed) male Fischer 344 rats.

14. Biotransformation of Sevoflurane in male Sprague-Dawley rat liver slices. Payne et al, *ISSX Proceedings* 4:168, 1993. Liver slices prepared from Curidine (200 mg/kg, i.p., 1 day) treated animals exhibited greater induction of Sevoflurane biotransformation (~12 fold of control) than phenobarbital (80 mg/kg/day for 4 days) treated animals (~5 fold of control). The fluoride levels after incubation of Sevoflurane with liver slices prepared from 5 or 7 day rat pups were comparable with liver slices prepared from adults rats.

15. Biotransformation of Sevoflurane in dogs and rats. Martis et al, *Anesthesia and Analgesia* 60:186-191, 1981. A comparison of the serum fluoride concentrations between the Sprague-

Dawley rat and mongrel dog indicated that the amount of sevoflurane metabolized was lower in the dog.

primary pharmacokinetic and metabolic studies of Sevoflurane in dogs.

February 9, 1978. Reference is made to IND reviewed by Clyde G. Oberlander on Sept. 5, 1978, page 10.

17. A new inhalation anesthetic. Wallin et al, *Anesthesia and Analgesia* 54:758-765, 1975. The initial evaluation of sevoflurane has been discussed in this article.

18. Comparative in vivo evaluation of Sevoflurane, Halothane, Methoxyflurane and Isoflurane in Sprague-Dawley rats (IND Section 6, pp. 33-38, May 31, 1978). Sprague-Dawley rats were anesthetized for a single 5 hour period either with halothane (1.5-3.0%), methoxyflurane (0.7-1.0%), isoflurane (0.25-3.0%), or sevoflurane (2.0-3.0%). Methoxyflurane produced an increase in the urinary excretion of inorganic fluoride for several days. In contrast, sevoflurane and isoflurane produced increase in the urinary fluoride excretion for the first 24 hours after anesthesia but not after subsequent days. Halothane did not cause any significant change in fluoride excretion

19. A comparison of the renal effects and metabolism of Sevoflurane and Methoxyflurane in enzyme-induced rats. Cook et al, *Anesthesia and Analgesia* 54:829-835, 1975. Reviewed by Clyde Oberlander under IND page 26, October 21, 1976.

20. Renal effects and metabolism of Sevoflurane in Fisher 344 rats: An in vivo and in vitro comparison with Methoxyflurane. Cook et al, *Anesthesiology* 43:70-77, 1975. Reviewed by Clyde Oberlander under IND page 25, October 21, 1976

21. Renal function after Sevoflurane or Enflurane anesthesia in the Fisher 344 rat. Malan et al, *Anesthesia and Analgesia* 77:817-821, 1993. One year old Fischer 344 rats were anesthetized with 10 minimal alveolar anesthetic concentration hours sevoflurane or enflurane with or without pretreatment with biotransformation enhancing agents (phenobarbital, ethanol or isoniazid). Sevoflurane did not effect the maximal urinary concentrating ability and did not enhanced the excretion of N-acetyl  $\beta$ -glucosaminidase in the urine in non-induced or enzyme-induced rats. Enflurane produced laboratory evidence of nephrotoxicity under similar conditions.

22. Metabolic and toxicologic studies with Enflurane in Swiss/ICR mice. Baden et al, *J Environmental Pathology and Toxicology* 4:293-303, 1980. The in vitro rate of defluorination of enflurane was compared to that of methoxyflurane, isoflurane and sevoflurane. No dose-response relationship was evident in these metabolic and toxicologic studies.

23. Sevoflurane is biotransformed by guinea pig liver slices but causes minimal cytotoxicity. Ghantous et al, *Anesthesia and Analgesia* 75:436-440, 1992. Sevoflurane (2.1 mM) and isoflurane (2.3 mM) had no effect on adult male Hartley guinea pig liver slices  $K^+$  content, but depressed protein synthesis (40-50% of control) after a 24 hour incubation period under 95% oxygen. The biotransformation of sevoflurane was maximal at 95%  $O_2$ , with three-fold more F produced from

sevoflurane than isoflurane.

24. Sevoflurane biotransformation and hepatotoxicity in the guinea pig. Lind et al, *Anesthesiology* 71:A310, 1989. Sevoflurane did not show direct cytotoxic actions as in vitro tissue slices showed no loss of  $K^+$  over 24 hours and in vivo exposure did not produce lesions typical of hepatotoxic agents. The increase in ALT (2-3 fold) was associated with areas of liver necrosis typical of ischemia or low oxygen tension.

25. Dose-related Sevoflurane metabolism to inorganic fluoride in rabbits. Hossain et al, *Hiroshima J Med Sci*, 40:1-7, 1991. The formation and excretion of fluoride ion after sevoflurane anesthesia was dependent on the sevoflurane dose. The authors also concluded that 1-3% of sevoflurane for 2 hours of incubation is unlikely to produce renal dysfunction.

26. Ethanol-inducible cytochrome P450 in rabbits metabolizes Enflurane. Hoffman et al, *British Journal of Anesthesia* 63:103-108, 1989. Imidazole (200 mg/kg/day, i.p., for 4 days) produced a 250% increase in the hepatic microsomal metabolism of enflurane, sevoflurane, methoxyflurane and the control substrate, aniline in male New Zealand rabbits (2-2.5 Kg body weight).

27. Comparison of MAC and the rate of rise of alveolar concentration of Sevoflurane with Halothane and Isoflurane in the dog. T. Kazama and K. Ikeda, *Anesthesiology* 68:435-437, 1988. The MAC values for sevoflurane, isoflurane and halothane were  $2.36 \pm 0.46\%$  ( $n = 18$ ),  $1.39 \pm 0.25\%$  ( $n = 10$ ), and  $0.89 \pm 0.20\%$  ( $n = 12$ ), respectively, in mongrel dogs (7.5-15.0 kg).

28. Pharmacokinetics of Desflurane, Sevoflurane, Isoflurane, and Halothane in pigs. Yasuda et al, *Anesthesia and Analgesia* 71:340-348, 1990. Five young female swine (3-4 months, ~20 kg) received simultaneously approximately one-third the MAC of each of desflurane, isoflurane, sevoflurane, and halothane for 30 minutes via a non-rebreathing circuit. The recoveries of desflurane ( $93 \pm 7\%$ ) and sevoflurane ( $111 \pm 17\%$ ) were not different from that of isoflurane (100%), but the recoveries of all three anesthetics were greater than that of halothane ( $77 \pm 6\%$ ).

29. Volatile anesthetics compete for common binding sites on bovine serum albumin. A  $^{19}F$ -NMR study, Dubois et al, *Proc. Natl Acad Sci* 90:6478-6487, 1993. The similarity of the  $K_d$  and  $K_s$  for halothane, sevoflurane and methoxyflurane indicated that they were competing with isoflurane for binding at the fatty acid-displaceable domains.

30. Clinical characteristics and biotransformation of Sevoflurane in healthy human volunteers. D.A. Holaday and F.R. Smith, *Anesthesiology* 54:100-106, 1981. Sevoflurane produced anesthesia in six healthy volunteers and showed limited biotransformation with minor systemic toxicity.

31. Uptake, elimination and biotransformation of volatile anesthetics in humans: A comparative study of Sevoflurane with Halothane, Enflurane, and Isoflurane.

unpublished report, October 1986. The advantages of sevoflurane over halothane, enflurane and isoflurane seemed to be rapid induction and emergence of anesthesia in 32 male and female patients.

32. Comparison of the kinetics of Sevoflurane and Isoflurane in humans. Yasuda et al, *Anesthesia and Analgesia* 72:316-324, 1991. The metabolism of sevoflurane and isoflurane and the elimination from tissues did not differ, but the ratio of FA/FI increased and the FA/FAO ratio decreased more rapidly for sevoflurane than isoflurane in seven healthy male volunteers.
33. Plasma inorganic fluoride with Sevoflurane anesthesia: Correlation with indices of hepatic and renal function. Frink et al, *Anesthesia and Analgesia* 74:231-235, 1992. Sevoflurane (50 patients) or isoflurane (25 patients) was administered with a semiclosed circle absorption system (total gas flow 2 L/min oxygen) for 1.0 to greater than 7.0 MAC hours during surgical anesthesia. Prolonged sevoflurane anesthesia in 5 patients led to peak fluoride levels that transiently exceed 50  $\mu\text{mole/L}$ . No increases in postoperative levels of creatinine, blood urea nitrogen, direct bilirubin or hepatic transaminase occurred in any anesthetic group. There was no evidence of renal dysfunction in any of the patients anesthetized with sevoflurane. The effect on the renal-concentrating ability after sevoflurane was not evaluated in this study.
34. Serum and urinary inorganic fluoride concentrations after prolonged inhalation of Sevoflurane in human. Kabayshi et al, *Anesthesia and Analgesia* 74:753-757, 1992. The present study in ten patients without renal disease demonstrated the significantly higher concentrations of serum ( $42.5 \pm 4.5 \mu\text{mole/l}$ ) and urinary inorganic ( $1804 \pm 378 \mu\text{mol/day}$ ) fluoride after exposure to lengthy sevoflurane anesthesia (10-19 hours). Those increases were rapidly abolished most likely because of rapid excretion through the lungs and kidneys.
35. Phase I clinical study- identification of the urinary metabolite of Sevoflurane in man by GC-MS. Imai et al, Maruishi Pharmaceutical Co., Ltd. report, August 1986. A gas chromatographic-mass spectrometric (GC-MS) method for the quantification and identification of hexafluoroisopropanol (HFIP) in  $\beta$ -glucuronidase treated human is described in this paper.
36. Urinary excretion of hexafluoroisopropanol glucuronide and fluoride in patients after Sevoflurane anesthesia. Gazing et al, *Journal of Pharmacy and Pharmacology* 45:67-69, 1993. The urinary excretion half-life for HFIP glucuronide in six surgical patients, without evidence of hepatic or renal impairment, was estimated to be 54.9 hours. The urinary excretion half-lives for inorganic fluoride and organic fluoride were 34.5 hours and 67.1 hours, respectively.
37. Identification of cytochrome P450 2E1 as a predominant enzyme catalyzing human liver microsomal defluorination of Sevoflurane, Isoflurane, and Methoxyflurane. Kharsch et al, *Anesthesiology* 79:795-807, 1993. Cytochrome P450 2E1 was the principal human liver microsomal enzyme catalyzing the defluorination of sevoflurane. The order of anesthetic metabolism by human liver microsomes was methoxyflurane > sevoflurane > enflurane > isoflurane > desflurane > 0, as assessed by fluoride production at saturating substrate concentrations.
38. Partition coefficients for Sevoflurane in human blood, saline, and olive oil. D.P. Strum and E.I. Eger II, *Anesthesia and Analgesia* 66:654-656, 1987. The blood/gas partition coefficient of  $0.686 \pm 0.047$ , a saline/gas partition coefficient of  $0.370 \pm 0.016$ , and an oil/gas partition coefficient of  $47.2 \pm 2.7$  for sevoflurane was found in 19 patients.

39. Solubility of I-653, Sevoflurane, Isoflurane and Halothane in human tissue. Yasuda et al, *Anesthesia and Analgesia* 69:370-3, 1989. The order of tissue/blood partition coefficient was halothane > sevoflurane > isoflurane > I-653. The order of the tissue/gas partition coefficient was halothane > isoflurane > sevoflurane > I-653.

40. Synthesis of fluoro-deuteriomethyl 1,1,1,3,3,3-hexafluoro-2-propyl ether (deuterated Sevoflurane). Baker et al, *J Labelled Compounds and Radiopharmaceuticals* 33:801-807, 1993. Sevoflurane was synthesized with deuterium substituents on the fluoromethoxy carbon.

#### Summary and Evaluation of ADME Studies

Sevoflurane was hardly metabolized in Wistar rats and its blood/gas partition coefficient was 0.6. Therefore, the induction and emergence of the anesthesia produced by this agent are expected to be very rapid. In Sprague-Dawley rats, the alpha-phase elimination rates for sevoflurane from blood and brain were approximately twice that of halothane. The beta-phase elimination rates for both volatile anesthetics were similar in brain and in blood. Xu et al (*Anesthesiology* 79: a414; 1993) had demonstrated the feasibility of using <sup>19</sup>F-MRI to characterize the regional distribution of sevoflurane (fluorinated general anesthetics) in rat brain.

The rates of metabolism of sevoflurane and deuterated sevoflurane in rat liver microsomes and whole animals were compared by Baker et al (*Drug Metabolism and Disposition* 1993; 21: 1170-1171). The results showed that substitution of the two hydrogens on the fluoromethoxy group of sevoflurane with deuterium substantially (~90% in vitro) inhibits metabolism of this molecule. The decreased metabolism of deuterated sevoflurane in rats may be an indication that the initial enzymatic attack involves insertion of oxygen on the methoxy moiety, with subsequent cleavage of the ether linkage and release of a single fluoride ion.

The renal effects of sevoflurane and enflurane in Fischer 344 rats have been compared by Malan et al. (*Anesth Analg* 1993; 77:817-821). Hepatic cytochrome P-450 system inducers were used to enhance metabolism of anesthetics in order to obtain serum fluoride concentrations equivalent to humans. Sevoflurane at 10 MAC-hours produced no evidence of fluoride-induced nephrotoxicity (maximal urinary concentrating ability and effect on N-acetyl  $\beta$ -glucosaminidase) in non-induced or enzyme-induced Fischer 344 rats. In contrast, enflurane produced laboratory evidence of nephrotoxicity. Contribution of factors such as systemic hemodynamics, renal blood flow or tubular sensitivity to fluoride have not been investigated in this paper.

In humans, Sevoflurane is biotransformed to hexafluoroisopropanol (HFIP) with the release of inorganic fluoride and carbon dioxide. HFIP is rapidly conjugated with glucuronic acid (Phase II biotransformation) and eliminated as a urinary metabolite. P450 2B, the major family of cytochrome P450 induced by phenobarbital in rats, rabbits, and guinea pigs is expressed minimally in human liver. Other cytochrome families that are inducible in human by phenobarbital, P450 3A and P450 2C, do not metabolize sevoflurane. Therefore, the induction of sevoflurane, enflurane and isoflurane metabolism in rats and rabbits by phenobarbital and phenytoin is expected to have negligible influence by these inducers on the metabolism of these agents in human.

**(III). Toxicology****Toxicology Studies****A. Acute Inhalation Toxicity Studies:**

1. Acute toxicity studies in four species (IND 21, 1976, page 10, by Clyde Oberlander.. This study was reviewed on Oct. 21, 1976, page 10, by Clyde Oberlander..
2. Inhalational acute toxicity study of Sevoflurane in mice. M.Tamada, Central Research Laboratories, Maruishi Pharmaceutical Co., Ltd. Study SEVO-4A27; (1985). The LC<sub>50</sub> values following a 3-hour inhalation exposure to ICR mice were 2.83% for males and 2.87% for females. Main acute signs were suppression of respiration and cyanosis.
3. An acute toxicity study of Sevoflurane in neonatal mice. M.Tamada, Central Research Laboratories, Maruishi Pharmaceutical Co., Ltd. Study SEVO-5A27; (1986). After three hours inhalation of sevoflurane, the LC<sub>50</sub> values in seven day old ICR mice were 4.48% (4.20 - 4.79%) and 4.50% (4.04 - 5.00%) for males and females, respectively. The LC<sub>50</sub> values for sevoflurane in 14 days old mice were 3.31% (2.92 - 3.76%) for male and 3.34% (3.06 - 3.65%) for female mice. Cyanosis leading to dyspnea was the primary cause of death.
4. Inhalational acute toxicity study of Sevoflurane in rats. M.Tamada, Central Research Laboratories, Maruishi Pharmaceutical Co., Ltd. Study SEVO-4A37; (1985). The LC<sub>50</sub> values following a 3-hour inhalation exposure to Wistar rats were 2.68% (2.81 - 2.95%) for male and 2.95% (2.79 - 3.11%) for female rats. Dyspnea and cyanosis were the main causes of death.
5. Acute toxicity of Sevoflurane in neonatal rats at seven days of age by inhalational administration. Y. Kawai, Central Research Laboratory, Maruishi Pharmaceutical Co., Ltd. (1990). The inhalation LC<sub>50</sub> values of sevoflurane dosed for 3 hours was 4.8% (4.5 - 5.4%) in males and 4.2% (3.9 - 4.5%) in females. Loss of righting reflex and oligopnea were observed.
6. An acute inhalation study of Sevoflurane in cynomolgus monkeys. W.Tierney, Bio/dynamics Inc. Report 84-2815;(1985). Originally reviewed by Clyde Oberlander under IND page 18, dated February 27, 1986. The lethal dose of sevoflurane following a 3-hour exposure period was estimated to be 6-8% end tidal concentration (3 to 4 MAC).

**B. Acute Oral Toxicity Studies:**

1. Acute toxicity study of Sevoflurane administered orally in mice. M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Ltd., Study SEVO-6A21;(1986). After a single gavage dose of sevoflurane (specific gravity 1.521) to ICR mice, the LD<sub>50</sub> values were 24.3 ml/kg (21.9 - 27.1 ml/kg or 33.3 - 41.2 mg/kg) for males and 18.2 ml/kg (16.7 - 19.8 ml/kg or 25.4 - 30.1 mg/kg) for females. Deaths occurred within 24 hours after administration. Loss of righting reflex, suppression of respiration, opisthotonos and piloerection were observed.

2. Acute toxicity study of Sevoflurane administered orally in rats. M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-6A31;(1986). The LD<sub>50</sub> values following a single oral gavage dose to Wistar rats were 16.6 ml/kg (12.3 - 22.5) for male and 10.8 ml/kg (9.6 - 12.1) for female rats.

#### C. Acute Intraperitoneal Toxicity Studies:

1. Acute toxicity study of Sevoflurane administered intraperitoneally in mice. M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-6A24;(1986). The acute intraperitoneal LD<sub>50</sub> values in ICR mice were 11.7 ml/kg (10.2 - 13.4) for male and 10.5 ml/kg (8.3 - 13.4) for female mice. Toxic signs were decreased locomotor movement, staggering gait, loss of righting reflex, suppression of respiration and piloerection.

2. Acute toxicity study of Sevoflurane administered intraperitoneally in rats. M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-6A34;(1986). The LD<sub>50</sub> value was 7.4 ml/kg (6.2 - 8.9) in male and 6.3 ml/kg (5.3 - 7.4) in female Wistar rats.

#### Summary of Acute toxicity

The results of acute toxicity studies performed with sevoflurane are summarized below:

Species	Strain	Mode of Administration	Exposure duration (hours)	LC <sub>50</sub> (%) or LD <sub>50</sub> (ml/kg) [male/female]
Mouse	NR	Inhalation	1	8.3%
Mouse	ICR	Inhalation	3	2.83 - 2.87%
Mouse	ICR	Inhalation	3	7-day old: 4.48/4.50% 14-day old: 3.31/3.34%
Mouse	ICR	Oral	-	24.3/18.2 ml/kg
Mouse	ICR	Intraperitoneal	-	11.7/10.5 ml/kg
Rat	NR	Inhalation	1	5.8%
Rat	Wistar	Inhalation	3	2.88/2.95%
Rat	Wistar	Inhalation	3	4.8/4.2%
Rat	Wistar	Oral	-	16.6/10.8 ml/kg
Rat	Wistar	Intraperitoneal	-	7.4/6.3 ml/kg
Rabbit	NR	Inhalation	1	10.6%
Dog	NR	Inhalation	1	7.3%
Monkey	Cynomolgus	Inhalation	3	6.0 - 7.9%

NR = Not reported

The LC<sub>50</sub> value for sevoflurane in young mice (~ 3.3% following a 3-hour inhalation) was higher than that of the adult mice (~2.8% following a 3-hour inhalation) indicating the weaker acute toxicity to the young mice. The LC<sub>50</sub> value for rats at age 5 weeks (~2.9%) was also lower than neonatal (=4.5%) rats indicating that neonatal rodents are more tolerant to acute exposure of sevoflurane than adults.

Toxic signs observed during preclinical acute studies (dyspnea, cyanosis) may be due to suppression of the central nervous system, the principal action of the test article (sevoflurane). Lung and liver congestion were noted in a number of studies but no dose-dependency was observed.

#### Subchronic Repeated Dose Studies

1. Eight week inhalational subacute toxicity study of Sevoflurane in rats. M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-4S37; (1987). This study has been previously reviewed by Clyde Oberlander under INI on Feb. 27, 1986.
2. Two week subacute toxicity study in dogs. (IND Reference is made to IND reviewed by Clyde Oberlander, dated Oct. 21, 1976, page 14.
3. Subacute inhalation studies of Sevoflurane and Halothane in *Macaca speciosa*. 1977 (IND Reference is made to IND reviewed by Clyde Oberlander, dated Sept. 5, 1978, page 3.
4. An eight week inhalation toxicity study of Sevoflurane in cynomolgus monkeys Report 84-2866;(1985). Reference is made to IND reviewed by Clyde Oberlander, dated Feb. 27, 1986, page 25.

#### Summary of Subchronic Toxicity

An 8 week subacute inhalation toxicity study of sevoflurane (0.1, 0.22, 0.5 and 1.0 MAC) and enflurane (1 MAC), administered 3 hours daily, 3 days per week, with a two week recovery period was conducted in SPF Wistar rats. Male and female SPF Wistar rats of the 0.5 and 1.0 MAC sevoflurane groups displayed a dose-dependent reduction in the body weight gain which persisted during the recovery period with slight restoration. Sevoflurane treated females showed a dose-dependent increase in ALP. Dose-dependent changes in brain, thymus, liver, spleen and thyroid weight (absolute and/or relative weight) were observed in both males and females treated animals but generally not seen at the end of the recovery period. No apparent drug-related histopathology was observed.

Male and female beagle dogs were exposed to surgical concentrations of sevoflurane (5-8%), 3 hours daily, 5 days per week for 2 weeks with controlled (16-20 per minute) or spontaneous respiration. A semi-closed rebreathing system with CO<sub>2</sub> absorbent was used to administer sevoflurane with a total gas flow of 500 ml/min. Respiration was depressed, respiratory acidosis occurred, rectal temperature decreased three degree C, and EEG decreased in amplitude and frequency with increased depth of anesthesia. Bradycardia requiring treatment with atropine

occurred in five of the eight exposed dogs (more frequently seen in halothane treated animals). Arterial blood pressure remained normal. There was no ventricular fibrillation in sevoflurane treated dogs in response to epinephrine challenge as opposed to halothane treated animals. Premature ventricular contractions occurred in 5/8 dogs. Both sevoflurane and halothane treated groups showed focal pulmonary atelectasis and vacuolization of parenchymal cells of the liver.

An eight week inhalation toxicity study of sevoflurane (1, 1.6 and 2.5 MAC) administered daily for three hours, 3 days per week in a close rebreathing system with CO<sub>2</sub> absorbent was conducted in cynomolgus monkeys. Three high dose animals died (two spontaneous deaths on days 5 and 10; one euthanized in extremis on day 30). SGOT, SGPT and LDH were increased in a dose-related manner and did not return to normal value until weeks 4, 6, 8, respectively, in high dosed animals. Urinary inorganic fluoride levels in sevoflurane treated animals reached the highest level (3 - 5 times pre dose) during the first week of exposure and were found throughout the study period. The thymus weights were increased in low, mid and high dose males. Body weights, hematology, urinalysis, rectal temperature and gross and histopathology showed no apparent drug-related toxic effects in monkeys.

#### Developmental and Reproductive Toxicity Studies

##### Inhalation Studies:

1. Toxicity study of Sevoflurane given prior to and in the early stages of pregnancy in rats. M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-4R3A;(1986). Sevoflurane was administered by whole body inhalation without CO<sub>2</sub> absorbent to male (137 - 175 g body weight, 6 weeks old) and female (132 - 185 g body weight, 11 weeks of age) Sic-Wistar rats before mating, and to females in the early stages of pregnancy. Males were exposed for 64 days before mating. Females were exposed from day 14 before pregnancy until the day 7 of gestation. An open (whole body) system without a CO<sub>2</sub> absorbent was used for exposure at 0.1 (0.22%), 0.3 (0.66%), 0.5 (1.1%), and 1.0 MAC (2.2%, Lot number C12) for three hours per day every other day. Ethrane group of 0.5 MAC (0.75%) was used as a comparative control. Each dose group consisted of 20 males and 20 females. The effects on the reproduction and on fetuses were examined.

##### Results:

**Effects on males:** Two animals in the 1 MAC group died due to accidental suffocation. General signs observed were staining around the anus and diarrhea in a sporadic manner. The body weight gain in the 0.5 and 1.0 MAC males was depressed in a dose-dependent manner. Hepatic tumor was detected in one animal in 0.3 MAC group and two each in 0.5 and 1 MAC groups. Hypertrophy of cervical lymph nodes was observed in two animals in 0.1 MAC and three in 0.5 MAC groups of sevoflurane. Organ weights of prostate and testis were affected in a non dose-dependent manner.

**Effects on females:** Staining around the anus, diarrhea and staining of the vulva with urine were observed. Body weight gain was suppressed in 0.3, 0.5 and 1.0 MAC females in a dose-dependent manner, during the two weeks of sevoflurane administration. Hepatic tumor was detected in two animals in 0.3 MAC group and one each in other inhalation groups. Opaque eyes were observed in two animals in 1 MAC group.

**Effects on copulation and fertility:** The copulation rate was low in most treated groups. No

differences in the number of corpora lutea and implantation were observed. Skeletal variations in 1 MAC sevoflurane fetus (separation of thoracic vertebral body, extra lumbar vertebra) were higher than that of the control.

2. Toxicity study of Sevoflurane given during the period of fetal organogenesis in rats. M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-5R3B;(1986). Six-Wistar male rats weighing 200-300 g and females weighing 120-180 g were used for mating. One hundred and sixty-two mated females were divided into 5 groups (32-33 animals/group) as shown below.

Administration Group	Pregnant	Number of animals for caesarean section	for littering
Control	32	20	12
0.1 MAC Sevoflurane	33	22	11
0.3 MAC Sevoflurane	32	20	12
1.0 MAC Sevoflurane	33	22	11
1.0 MAC Ethrane	32	21	11

An open system without a CO<sub>2</sub> absorbent for sevoflurane (Lot number 13) and Ethrane (enflurane, positive control, Lot number 69036TT) exposure (three hours/day) at a gas flow rate of 6 L/min during gestation day 7 to 17 (11 consecutive days) was used. The control group was exposed to the vehicle gas, oxygen.

#### Measurements and Observations:

##### 1 - F<sub>0</sub> Maternal

###### Daily

Gestation days 0, 4, 7, 14, 21

and lactation days 0,7,14,21

Gestation day 0 - sacrifice

Gestation day 20

Survival, appearance, behavior

Maternal Body Weights, food consumption

Water consumption

Gross Necropsy

##### 2 - F<sub>1</sub> Fetuses

Gestation day 20

Weight, sex

visceral examination (1/2 fetuses)

Skeletal examination (1/2 fetuses)

##### 3 - F1 Offspring

Lactation day 4

8 pups/litter selected for development and reproduction studies

Lactation day 35

Skeletal, necropsy examination, 1 M/F

Behavioral tests on lactation day indicated

Day 21-  
Day 28-  
Day 42-  
Day 49- 56

Sensory function  
Motor harmony  
Emotionality  
Learning ability

4 - F, Adult

Day 70  
Gestation day 20 (F1)  
Offspring (F1) at 12 weeks of age

Selection for testing and mating, M/F  
Gross Necropsy  
Necropsy, M/F

Statistical analysis: t test

Results:

1. F<sub>0</sub> Maternal Observations:

- (i) General signs: No difference (diarrhea, loose stools)
  - (ii) Body weight: Caesarean section groups - Suppressed in 0.3, 1.0 MAC sevoflurane and 1 MAC ethrane groups.  
Littering groups - Lower values in all treated groups.
  - (iii) Food and water intake: Reduced in all treated groups (caesarean and littering groups), significantly reduced in 1 MAC exposed dams.
  - (iv) Macroscopic findings at necropsy of dams after caesarean section:
    - Control - liver tumor (2/20 animals)
    - 0.1 MAC sevoflurane - Retention of tissue fluid in the right ovarian bursa (1 animal)
    - 0.3 MAC sevoflurane - Liver tumor (1/20 animal), Retention of tissue fluid in the left ovarian bursa (1 animal)
    - 1.0 MAC sevoflurane - Retention of tissue fluid in the left ovarian bursa (1 animal)
    - 1.0 MAC ethrane - Retention of tissue fluid in the left ovarian bursa (2 animals)
- Macroscopic findings at necropsy of dams after weaning:  
0.1 MAC sevoflurane - One liver tumor  
1.0 MAC sevoflurane - One case of fluid retention in the left ovarian bursa.

2. Effects on fetuses (F1):

- General - No difference in the mean number of corpora lutea, number of implantation, implantation rate, the number of live fetuses, the embryo lethality and sex ratio between the control and treated groups.
- Body weight: 1.0 MAC sevoflurane and ethrane groups - Reduced
- External and visceral observation: No difference
- Skeletal examination: 1.0 MAC sevoflurane and ethrane - Increased number of fetuses with skeletal variations. Increased lumber rib in ethrane group. Sternebrae and total bone number in forelimbs significantly reduced.
- Effects on delivery and nursing: No difference in number of implantation, the mean number of live newborns, the sex ratio, the birth rate, the survival rate and the weaning rate.

**3. Effects on offspring (F1):**

- Body weight from birth to 10 weeks of age:** Suppressed bodyweight gain in 1 MAC sevoflurane (6% in ♂, 5% in ♀) and ethrane (4% in ♂, 3% in ♀),
- Growth and development:** Eyelids opening was slower in 1 MAC group. Incisor eruption and descent of testis were slower in ethrane group.
- Function and motor harmony tests:**
- Visual placing reflex test - Non-reactive animals 1 in 1 MAC group.
  - Auditory, pinna, surface or air righting reflex and rotor rod test - No difference
- Emotionality test:** No difference in ambulation, rearing, facing, grooming and defecations.
- Learning ability test:** Shuttle box and water T-maze tests - No difference
- Skeletal examination:** Abnormality of caudal vertebrae in one animal each of 0.3 & 1 MAC.
- Hematological examination:** Increased hemoglobin in 0.3 MAC and ethrane groups.
- Necropsy (F1 - 5 weeks old):**
- Control - Liver tumor (2/12♀), congestion of submaxillary lymph node (1♂)
  - 0.1 MAC sevoflurane - Congestive thymus (2♂), congestion of submaxillary lymph node (1♂)
  - 0.3 MAC sevoflurane - congestion of submaxillary lymph node (1♂), congestive thymus (2♀), hyperemia of submaxillary lymph node (1 ♀).
  - 1 MAC sevoflurane - Liver tumor (2/10 ♂, 2/9♀) hyperemia of submaxillary gland (1♂)
  - 1 MAC ethrane - Congestive thymus (1♂, 1 ♀), liver tumor (1♀)
- Organ weights:** No dose-related effect

**4. F1 Adults:**

- Reproductivity test :** No difference in copulation, impregnation and conception rates
- Body weight of F1 in gestation period:** Decreased dose-dependently but no significant differences.
- Caesarean section of F1 dams at last stage of gestation:-** No difference except liver tumor in 1/6 dam of 0.1 MAC and 3/6 dams of 1 MAC sevoflurane. Liver tumor in 1/6 dam in ethrane group.
- Skeletal examination of fetuses (F2) -** No difference in skeletal variation in treatment groups from those in the control.
- Blood analysis of F1 at 12 weeks of age -**
- 0.1 MAC sevoflurane -Hematocrit value (5% ↓ in ♂, creatinine (7% ↓ in ♀), WBC (32% ↓ in ♀)
  - 0.3 MAC sevoflurane - Blood urea nitrogen (10% ↓ in ♂)
  - 1 MAC sevoflurane females - RBC (5% ↓ in ♀), hemoglobin (4% ↓ in ♀), total protein (5% ↓ in ♀) and creatine (8% ↓ in ♀)
  - Ethane - Hemoglobin (5% ↓ in ♂), GTP (1 in ♂), creatinine (4% ↓ in ♂), albumin (7% ↓ in ♂)
- Organ weights of F1 at 12 weeks of age:** 0.3 MAC - reduced pituitary,  
1.0 MAC - Reduced pituitary, brain (♀)  
Ethane - Reduced spleen and thyroid , brain (♀)
- Necropsy of F1 at 12 weeks of age:**
- Control - liver tumor (1/6♂, 2/6 ♀), hyperemia of the lymph node (1♂), thymus congestion (1♂)
  - 0.1 MAC -Hyperemia of the lymph node (1♂), thymus congestion (2♂)
  - 0.3 MAC - Liver tumor (1/6♂), thymus congestion (2♂)
  - 1 MAC - hyperemia of the lymph node (4♂), thymus congestion (1♂), hyperemia spots in thymus (1♀)
  - Ethane - Liver tumor (1♀), hyperemia of the lymph node (2♂), thymus congestion (1♂)

**3. Teratogenicity study of Sevoflurane, an inhalational anesthetic, in rabbits (segment II test).**

(1986). Ninety inseminated Japanese White rabbits (2.8 - 3.9 kg, 3 months or older) were distributed to the groups as shown below. Drugs were administered with an inhalation mask three hours daily at a fixed time from day 6 to day 18 of gestation. An open system without a CO<sub>2</sub> absorbent was used for exposure. The animals were observed daily for general symptoms and killed on day 29 of gestation. Thoracic and abdominal organs were examined macroscopically.

Groups	Dose	Animals used	Pregnant
Group A	High dose of sevoflurane (1 MAC; 1.8% in O <sub>2</sub> )	18	15
Group B	Medium dose of sevoflurane (0.33 MAC; 0.6% in O <sub>2</sub> )	18	15
Group C	Low dose of sevoflurane (0.1 MAC; 0.18% in O <sub>2</sub> )	18	13
Group D	Comparative control (ethrane 1 MAC; 1.32% in O <sub>2</sub> )	18	15
Group E	Vehicle control (O <sub>2</sub> only)	18	16
Group F	Control (no administration)	18	15

**Results: Effects on Dams:**

General symptoms - No significant clinical signs (diarrhea, sneezing, discharge from eyes etc.)

Mean body weight - High dose (6%↓), medium dose (5%↓)

Food intake - High dose (35%↓),

Water intake - High dose (28%↓)

Necropsy - No difference between control and inhalational groups.

Reproductive system - No effect

**Effects on Fetuses:**

External observation - No difference

Visceral observation - No significant abnormalities except one case of horseshoe kidney and one case of cleft palate were observed in ethrane group.

Skeletal observation - No significant abnormal cases.

**4. Toxicity study of Sevoflurane given during the perinatal and lactation period in rats. M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-5R3c;(1986). One hundred and thirty one pregnant SLC-Wistar rats were administered sevoflurane via whole body inhalation in an open system without CO<sub>2</sub> absorbent. The total rate of gas flow was 6 L/min. The animals were exposed three hours per day from Gestation Day 17 to Postnatal Day 21. The control group was exposed to the oxygen, the vehicle gas.**

Group	No. of Animals
Control	29
Sevoflurane 0.1 MAC (0.22%)	25
Sevoflurane 0.3 MAC (0.66%)	25
Sevoflurane 1 MAC (2.2%)	28
Ethrane 1 MAC	24

**Measurements:**

**1 - F<sub>0</sub> Maternal**

Daily  
Gestation days 0 - 20  
and lactation days 0,7,14,21  
  
Lactation day 20

Survival, appearance, behavior  
  
Maternal Body Weights, food consumption  
Water consumption  
Gross Necropsy

**2 - F<sub>1</sub> Offspring**

Lactation day 0  
Lactation day 4  
  
Lactation day 35

Weight, sex, external examination  
8 pups/litter selected for development and  
reproduction studies  
Selection for testing and mating, 20 M/F

**Behavioral tests on lactation day indicated**

Day 21-  
Day 28-  
Day 42-  
Day 49 - 56  
Day 35-  
Day 49-56

Sensory function  
Motor harmony  
Emotionality  
Learning ability  
Skeletal examination and necropsy  
Learning and memory

**3 - F<sub>1</sub> Adult**

Day 70  
Daily  
Gestation days 0,7,14,  
18, & 20  
Gestation day 20  
Day 84 of age of F1

Reproductivity test  
Survival, appearance, behavior  
  
Maternal Body Weights,  
Gross Necropsy, F<sub>2</sub> fetal examination  
Necropsy

**Results:**

**1. F<sub>0</sub> Maternal Observations:**

General symptoms - Staining around the anus or diarrhea in few animals, no significant differences,

Mortality: 0.1 MAC sevoflurane group - One due to miscarriage

1.0 MAC sevoflurane group - One due to suffocation

Mean body weight - No differences among groups

Food intake - No significant difference between the control and test groups.

Water intake - 0.1 MAC sevoflurane group - 10%

Reproductive system - No effect (sex ratio, implantation, birth rate, survival rate)

Necropsy - Control - Hepatic tumor (2 animals)

0.1 MAC - Hepatic tumor (2 animals), edema of left ovary (1 animal)

0.3 MAC - Hepatic nodule (1), pancreatic tumor (1 animal)

1.0 MAC - Hepatic nodule (1), enlarged heart (1), enlarged cecum (1), uterine edema (1)

## 2 - Effects on Fetuses:

Mortality: Control - 2♂; 1 MAC sevoflurane - 1♂ and 1♀; ethrane - 1♂

External observation - No difference with respect to sex ratio, birth rate and 4 day survival rate.

Body weight gain - 1 MAC sevoflurane - 6%, Ethrane - 10%

Development of offsprings: 0.1 MAC sevoflurane - Incisor eruption (5%)

0.3 MAC sevoflurane - Incisor eruption (6%), separation of auricle (16%)

1.0 MAC sevoflurane - Incisor eruption (6%), separation of auricle (12%)

Ethane - Descent of testes (4%)

Sensory function tests - No differences

After weaning:

Bodyweight: 1 MAC - Reduced (9% in ♂ and 3% in ♀)

Ethane - 10% in ♂ and 4% in ♀

Development: Ethrane - Testis descending delayed

Motor harmony test - No difference

General signs: Diarrhea, soft feces or staining around the anus, no significant difference.

Skeletal examination of F1 at 5 weeks of age: Ethrane - Caudal vertebrae (1/20)

Hematological examination - No difference in RBC, WBC, hemoglobin and hematocrit value.

Organ weights of offspring at 5 weeks of age:

0.1 MAC sevoflurane - spleen (7% in ♀)

1 MAC sevoflurane - Kidney (10% in ♂; 13% in ♀), liver (10% in ♂; 13% in ♀), heart (10% in ♂), brain (5% in ♂ & ♀), thymus (10% in ♂; 13% in ♀), lungs (17% in ♀)

Ethane - Kidney (14% in ♂; 13% in ♀), liver (13% in ♂; 17% in ♀), heart (13% in ♂, 9% in ♀), brain (5% in ♂ & ♀), spleen (10% in ♂; 21% in ♀), testes (14% in ♂; 13% in ♀)

Necropsy of F1 at 5 weeks of age:

Control - Opaque eye (1/10 in ♀), congestion of thymus (1/10 in ♀)

0.1 MAC sevoflurane - Opaque eye (1/10 in ♀), congestion of cervical lymph node (1/10 in ♀)

0.3 MAC sevoflurane - Opaque eye (1/10 in ♂), hepatic tumor (2/10 in ♀)

1.0 MAC sevoflurane - Opaque eye (1/10 in ♂), hepatic nodule (1/10 in ♂), congestion of thymus (1/10 in ♂ and 1/10 in ♀)

Ethane - Opaque eye (1/10 in ♂), congestion of thymus (1/10 in ♀)

Learning ability: No difference (shuttle box and water T-maze)

3 - Reproductivity of F1 at 10 weeks of age: 1 MAC sevoflurane - Reduced (5/10 vs 9/10)

Body weight at necropsy: 1 MAC sevoflurane - 8%, Ethrane - 7%

Caesarean section of dams F1: No difference

Hematology & biochemistry of F1 at 12 weeks of age:

0.3 MAC sevoflurane - Hemoglobin (3% ↓ in ♂), GOT (1 ↓ in ♂)

1.0 MAC sevoflurane - Hematocrit (5% ↓ in ♂), hemoglobin (3% ↓ in ♂)

Ethrane - GOT (7% ↓ in ♂), GPT (15% ↓ in ♂), ALP (8% ↓ in ♂)

Necropsy of F1 at 12 weeks of age:

Control: Congestion of cervical lymph node (1♂),

0.1 MAC: Hyperemia of cervical lymph node (1♂),

0.3 MAC: Hyperemia of submaxillary lymph node (1♂), thymus congestion (1♂), congestion of thymic lymph node (1♀)

1.0 MAC: Hepatic tumor (1♂), congestion of thymic lymph node (1♂),

Ethrane: Hepatic tumor (2♂), Congestion of cervical lymph node (1♀), congestion of submaxillary lymph node (2♀) and thymus congestion (1♀)

Organ weight of offspring (F1) at 12 weeks of age:

0.3 MAC sevoflurane - Liver (8% ↓ in ♂)

1.0 MAC sevoflurane - Liver (3% ↓ in ♂), kidney (7% ↓ in ♂), testes (6% ↓)

Ethrane - Kidney (8% ↓ in ♂), testes (5% ↓)

External and visceral examination of F2: No dose-related differences

#### Summary of Developmental and Reproductive Toxicity Studies

Sevoflurane did not effect ovulation and implantation during the early stage of pregnancy in rats. An open (whole body) system without a CO<sub>2</sub> absorbent at 0.1 (0.22%), 0.3 (0.66%), 0.5 (1.1%), and 1.0 MAC (2.2%) sevoflurane exposure every other day for three hours per day was used. Delayed ossification in 0.5 and 1 MAC group of sevoflurane may be a secondary effect of fetal growth suppression that was primarily attributed to the dose-dependent suppression of body weight gain by dams and fetuses. No effect levels for parent animals and next generation may be 0.1 MAC and 0.3 MAC, respectively.

Sevoflurane given without a CO<sub>2</sub> absorbent during fetal organogenesis (gestation day 7 to 17) in rats produced dose-dependent suppression of body weight gain during the early stage of drug administration. Clinical importance of liver tumor found in the animals (dams and offsprings) is unclear since the tumor was also detected in control animals and its histopathological examination showed no changes in liver parenchyma. According to the sponsor "The background data on Wistar rats from the same breeder indicated that the tumor in liver occurred spontaneously". The high incidence of total skeletal variation in 1 MAC and ethrane groups may be due to growth inhibition. Separation of sternebra, asymmetry of sternebra, and separation of thoracic vertebral body can be caused by delayed ossification. No drug related abnormalities were detected during external and visceral examinations. The no effect level of sevoflurane on dams appears to be 0.3 MAC.

The decrease in body weight gain of dams during teratogenicity study in rabbits (segment II) may be due to the stress at the forced inhalation, but not due to the toxicity of the sevoflurane at 1 MAC. The cleft lip (1/135 or 0.74%) in the high dose group is very low and comparable to the rate of spontaneous occurrence (0.38 - 1.87%). One case each of cleft palate and horseshoe kidney in ethrane group may suggest its teratogenicity. Teratogenic effects of sevoflurane without a CO<sub>2</sub> absorbent was not significant in rabbits.

The administration of sevoflurane by inhalation without a CO<sub>2</sub> absorbent to rats during the perinatal

and lactation periods did not effect the length of gestation period, mean number of implantations and mean number of offspring per dam. The bodyweight gains by offsprings of 1 MAC sevoflurane and ethrane groups were significantly reduced during 14 days after birth. Birth rate, sex ratio, external anomalies and nursing rate were not effected. Immature offsprings, diarrhea, and abnormal growth of incisor were not dose-dependent. Therefore, these effects may be regarded as accidental. The bodyweight of dams (F1) in the gestation period was not affected by sevoflurane. No significant difference in the number of corpora lutea, implantation and resorbed embryos per dam were observed. The no effect levels of sevoflurane in this study may be 0.3 MAC for dams (P) and offsprings (F1) and 1 MAC for fetuses (F2) at the last stage of gestation.

#### Mutagenicity studies

1. Mutagenicity study of Sevoflurane by use of microorganisms (Ames test). M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-5M1A;(1985). The mutagenicity of Sevoflurane was evaluated by Ames test using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA 1537 and TA1538 and *Escherichia coli* strain WP2uvr. The assay was conducted under sevoflurane vapor at 0.25, 0.5, 1.0, 2.0, 4.0, and 8% (v/v) concentration in the presence and absence of metabolic activator, S-9 mix. The number of the revertants of every tester strain was less than 2-fold of that in the negative control group and their was no dose-dependency.

2. Bacterial reverse mutation assay (Ames test plus *E. coli*) of Sevoflurane. M. Diehl, Drug Safety Evaluation Division, Abbott laboratories, TX93-076; R&D/93/450, (1993). *Salmonella typhimurium* bacteria (strains TA-1535, TA-1537, TA-98, TA-100 and TA-102) and *Escherichia coli* bacteria strain WP2uvrA- were used for the non-activated and rat liver microsome activated test. Sevoflurane was used over a range of five concentrations, 1 to 1000 ul per petri plate (1.8 to 166.7 ul/ml). The analysis indicated the concentration of sevoflurane between 0.42 to 0.79 ul/ml. This may be due to the volatility and limited solubility of sevoflurane in buffer. No toxicity or mutagenicity was observed in this assay.

3. Micronucleus test with mice of Sevoflurane. Y. Kawai, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-2M27; (1993). Male and female ddY mice (7 weeks old) were exposed to sevoflurane vapors at concentrations of 0.9, 1.8 or 3.5% for three hours/day for two consecutive days. The total rate of gas flow was 6 L/min. An open (whole body) system without a CO2 absorbent was used to expose the mice. Mitomycin was used as a positive control. Air (carrier gas) was used as negative control. A portion of femoral marrow cells suspension was used for observation of micronucleus and another portion was used for observation of reticulocyte. Sevoflurane did not show any evidence of clastogenic effects or inhibitory effect on hematopoietic function.

4. Chromosomal aberration test of Sevoflurane with mammalian cells in culture. T. Mizuno, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-5M1B; (1986). A fibroblast cell line (CHL/1U), established from the lung of a newborn Chinese hamster was used. Two negative controls, no exposure group and air exposure group, a positive control of MNNG group and three groups of sevoflurane (2, 4 and 8% v/v for 60 minutes of exposure) were employed. After the treatment cells were cultured for 24 hours or 48 hours. Chromosomal slides were prepared and examined for polyploidy and structural aberration as gaps, breaks, exchanges, inversion, fragmentation and ring formation. Sevoflurane exposed cells did not show any significant increase

of polyploids or structural aberration.

**5. Sevoflurane L5178YTK +/- mouse lymphoma mutagenicity assay.**

Microbiological Associates, Abbott Laboratories, TX93-210; R&D/93/725, (1993). Sevoflurane in DMSO was added directly to L5178Y TK +/- mouse lymphoma cell line. The maximum exposures to the cell cultures were 428-1037  $\mu\text{g/ml}$  and 64-811  $\mu\text{g/ml}$  without and with exogenous metabolic activation (rat liver S9), respectively. Sevoflurane inhibited the cell growth by 40% and 80% without and with exogenous metabolic activation, respectively, compared to control cultures. There was no evidence for any mutagenic activity of sevoflurane in this assay system.

**6. In vitro cytogenetics human lymphocyte culture assay of Sevoflurane.** M. Diehl, Drug Safety Evaluation Division, Abbott Laboratories, TX93-075; R&D/93/400, (1993). Human venous blood was cultured for approximately 44 to 48 hours before sevoflurane addition. The concentrations of test article were 0.01, 0.03, 0.1, 0.3, 1.0, 10 and 50  $\mu\text{l/ml}$ . Mitomycin C (0.125  $\mu\text{g/ml}$ ) and cyclophosphamide (12.5  $\mu\text{g/ml}$ ) were used as positive controls for the activation and non-activation tests. Toxicity was seen at the two higher concentration (10 & 50  $\mu\text{l/ml}$ ), which were too toxic to evaluate for chromosomal damage. Sevoflurane at 0.1, 0.3 and 1.0  $\mu\text{l/ml}$  did not show any increase in aberrant cells when compared to the untreated and vehicle control groups under activation or non-activation conditions.

**7. Mammalian cell transformation assay (Balb/c-3T3).**

Abbott Laboratories, TX93-211; R&D/93/876, (1993). Sevoflurane was solubilized in DMSO and added directly to BALB/3T3 cell transformation assay in the presence and absence of a metabolic activator. The measured concentration of sevoflurane ranged from 32.6 to 1360  $\mu\text{g/ml}$  in the beginning of the experiment and was not detectable in cell culture medium after three day incubation. Survival at the highest dose tested was 57% in the non-activated study and 55% in the S-9 activated study. No statistically significant increases in transformation frequency were observed in either the activated or non-activated test system.

**8. Sevoflurane  $^{32}\text{P}$  post-labeling DNA adduct assay in mouse liver.**

Abbott Laboratories, R&D/93/879, (1993). ICR mice (five males and five females per group, 22 to 26 g body weight) were exposed once by inhalation to 2.24%, v/v, (22,400 ppm) sevoflurane or filtered air for three hours. Dimethylnitrosamine (DMN) was administered intraperitoneally at 150 and 450 mg/kg as a positive control. Upon completion of the exposure period, blood samples were collected from each animal and livers were used for  $^{32}\text{P}$  post labeling assay.

The mice exposed to sevoflurane were unconscious during the three hour treatment interval, but recovered quickly after termination of exposure. Sevoflurane concentrations in the blood were 5.7  $\mu\text{g/ml}$  and 5.8  $\mu\text{g/ml}$  for males and females, respectively. DMN-treated animals demonstrated liver DNA-adducts. There were no DNA adducts detected in the sevoflurane-treated animals.

Summary of Mutagenicity Studies

Sevoflurane was non-mutagenic in bacterial reverse mutation assay (Ames assay). Sevoflurane exposed Chinese hamster lung fibroblast cell did not show any significant increase of polyploidy or

structural aberration at 2, 4 or 8% exposure concentration following 24 or 48 hours in culture. Sevoflurane did not produce clastogenic effects or inhibitory effect on hematopoietic function during micronucleus test in mice. Treatment with sevoflurane caused toxicity but no evidence for any transforming activity in the BALB/3T3 cell transformation assay was observed when tested in the presence and absence of exogenous metabolic activation. There was no evidence for any DNA adducts due to sevoflurane treatment during <sup>32</sup>P post-labelling DNA adduct assay in mouse liver. Since sevoflurane did not show any mutagenic effect in the above mentioned tests, it may be considered that sevoflurane is not mutagenic.

#### Special Toxicity Studies

##### Immunotoxicity:

1. Acute systemic anaphylaxis of Sevoflurane in guinea pigs. M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-5T47; (1985). Sixty-six male Hartly guinea pigs (~300 g body weight) were administered 1 MAC sevoflurane (2.9%) by inhalation for three hours, three times a day on day 1, 3 and 5 for sensitization and 1 MAC sevoflurane for 1 hour was administered once either on day 10 or on day 20 for challenge. An open whole body system without a CO<sub>2</sub> absorbent was used for exposure. Horse serum was used as a positive control. Antigenicity challenge (general anaphylaxis) was apparent in horse serum groups but not in sevoflurane or ethrane groups.

##### Hepatotoxicity Studies:

1. Evaluation of hepatotoxic potential of Sevoflurane in rats. Project No. CCS108A, Protocol 38-7, (1980). Male Sprague-Dawley rats (200 - 300 g body weight) were injected intraperitoneally with sesame oil (5 ml/kg), phenobarbital (50 mg/kg) or 100 mg/kg PCB as given below. Injections were given two times every day for four days. On the fifth day of treatment period, the animals were exposed for two hours to either oxygen, sevoflurane or halothane. An open system without CO<sub>2</sub> absorbent was used to administer sevoflurane.

Group	No of rats	Pretreatment	Treatment
1	9	Sesame oil	Oxygen
2	9	Sesame oil	2% Sevoflurane in oxygen
3	9	Sesame oil	1% Halothane in oxygen
4	9	Sesame oil + PCB	Oxygen
5	9	Sesame oil + PCB	2% Sevoflurane in oxygen
6	9	Sesame oil + PCB	1% Halothane in oxygen
7	9	Sesame oil + Phenobarbital	Oxygen
8	9	Sesame oil + Phenobarbital	2% Sevoflurane in oxygen
9	9	Sesame oil + Phenobarbital	1% Halothane in oxygen

Three animals from each group were sacrificed at 4, 24 and 48 hours after oxygen, sevoflurane or halothane exposure. Blood samples were collected for clinical chemistry evaluation. Livers were removed for histopathology and enzymology.

Pretreatment of rats with an enzyme inducer (PCB, phenobarbital) resulted in an increase in hepatic contents of cytochrome P-450 and NADPH-cytochrome c-reductase. SGOT and SGPT levels in rats pretreated with phenobarbital and exposed to either sevoflurane or halothane were not different from those proper controls. Hepatic tissues did not show any lesion associated with sevoflurane exposure.

2. Evaluation of hepatotoxic potential of Sevoflurane in guinea pigs, (1974). Gross and microscopic evaluation of hepatic tissues of guinea pigs (600 to 900 grams body weight) exposed to sevoflurane (2 - 2.5%) for 2 hours/day for four consecutive days did not reveal any abnormalities.

3. The effect on the liver of beagles by single inhalation of Sevoflurane.

(1989). Sevoflurane (4.2%), enflurane (3.7%) and halothane (1.6%) were inhaled at 1.8 MAC to beagle dogs (= 10 kg body weight, 4 animals/group). The animals were dosed with a mixture of pure oxygen (1 L/min) and air (4 L/min) as the carrier gas under controlled respiration with an artificial respirator set at 15 ml/kg per ventilation and a 12 times/min respiration rate.

General signs and symptoms did not change during the observation period. Time of awakening was =10 minutes with sevoflurane, =20 minutes with enflurane and =60 minutes with halothane. During anesthesia systolic and diastolic blood pressure was reduced by 49% with sevoflurane, 51% with enflurane and 32% with halothane. All values returned to normal values within 1 hour after the completion of anesthesia. A mild and transient increase in GOT, GPT, LDH and bilirubin was noted in all animals and returned to normal values in 48 - 72 hours. No toxic changes in livers were observed under the optical microscope.

4. Glucose study in dogs. 1978 (IND) Reviewed by  
Clyde Oberlander in IND page 9, on Sept. 5, 1978.

#### Irritation Studies

1. Eye irritation study in rabbits. (IND) Reference is made to  
IND review dated October 21, 1976, page 34.

2. Eye irritation test of Sevoflurane. M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Study SEVO-4T5A; (1985). Male Japanese white rabbits (= 2 kg body weight, eight animals per group) received either 0.1 ml sevoflurane or ethrane applied directly to one eye. The other eye served as an untreated control. Four animals from each group had their eye washed with 20 ml of lukewarm water four second after drug administration. The cornea, iris and conjunctiva of all eyes were examined at 1, 2, 4, 24, 48, 72, 95, and 168 hours after treatment. Slight conjunctival redness and /or edema-like swelling was observed in most of the rabbits in both

the washed and non-washed groups. All animals recovered within 95 hours of drug administration. According to the Kay & Calandra method, sevoflurane was classified as minimally irritating (M1), while the ethrane was classified as mildly irritating using the ocular mucous membrane stimulation classification..

#### Summary of special toxicity studies

Sevoflurane exposure for two hours did not show any signs of hepatic damage in male Sprague-Dawley rats pretreated with enzyme inducer (PCB or phenobarbital). No antigenic or adverse hepatic effect was found in sevoflurane treated male Hartly guinea pigs.

The hepatotoxic potential of sevoflurane exposure at 1.8 MAC (4.2%) was studied in beagle dogs. During exposure systolic and diastolic pressure was reduced by 49% and returned to normal values within one hour post-exposure. Sevoflurane did not induced gross or microscopic changes in the liver. All glucose values (days 1, 2, 7, 14, 16, and 28) were within normal range in mongrel dogs following a single acute 3 hour exposure to approximately 3-4% sevoflurane.

Ocular stimulation by sevoflurane was classified as mild according to the Kay & Calandra evaluation method.

#### Toxicity and Mutagenicity Studies of Hexafluoroisopropanol (HFIP)

##### A. Inhalation Studies:

1. An acute toxicity of hexafluoroisopropanol (HFIP) in rats by inhalational administration. M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Study HFIP-6A37; (1987). Slc:Wistar rats (-120 g body weight, 10/sex/group) received 0.13, 0.16, 0.17, 0.18, 0.19, or 0.20 % HFIP. An open system without CO<sub>2</sub> absorbent was used for a single three hour exposure. The total rate of gas flow was 6 l/min. The estimated LC<sub>50</sub> values were 0.185% (0.173 - 0.198) for males and 0.184 (0.178 - 0.189) for females. Pulmonary congestion and opaque eyes were observed in almost all rats which died. No treatment related findings were observed at necropsy in rats which survived inhalation.

##### B. Intraperitoneal Studies:

1. An acute toxicity of hexafluoroisopropanol (HFIP) in rats by intraperitoneal administration. M. Tamada, Central Research Laboratory, Maruishi Pharmaceutical Co., Study HFIP-6A34; (1987). The LD<sub>50</sub> of HFIP was 0.094 ml/kg (0.081 - 0.108) for male and 0.132 ml/kg (0.105 - 0.166) for female Slc:Wistar rats (-140 g body weight). Common findings in those rats which died during the experiment were congestion of the thymus, liver, lungs, and small and large intestine, as well as thymus atrophy and intestinal hemorrhage.

##### C. Intravenous Studies:

1. An acute toxicity of HFIP in rats by intravenous administration. Y. Kawai, Central Research Laboratory, Maruishi Pharmaceutical Co., Study HFIP-8A33; (1988c). The acute LD<sub>50</sub> values were 0.069 ml/kg (0.59 - 0.080) in male (=110 g body weight) and 0.071 ml/kg (0.061 - 0.082) for female (=100 g body weight) Wistar rats. Animals died during or within 5 minutes after the administration with reduced respiration rate and convulsion. No abnormality was observed upon hematological and serum biochemical examinations, urinalysis, organ weight and autopsy conducted at 14 days after the administration.

2. Seven days intravenous toxicity study of HFIP in rats. Y. Kawai, Central Research Laboratory, Maruishi Pharmaceutical Co., Study HFIP-8T3A; (1988d). Male and female Slc: Wistar rats (100 - 130 g body weight) received 0.025, 0.033 and 0.044 ml/kg HFIP (specific gravity - 1.59, Lot No. 17) for seven consecutive days. A control group received physiological salt solution. The dosage volume was 2 ml/kg and the rate of administration was 0.5 ml/min.

#### Results:

1. Clinical Observations: Soft feces or diarrhea, dysbasia or staggering gait, depressed locomotor movement in all treated animals
2. Mortality: 0.044 ml/kg - 2 ♂
3. Body Weight: 0.044 ml/kg - Decreased on days 3 & 7.
4. Food and Water Consumption: No difference
5. Hematology: 0.033 ml/kg - MCHC (4% ↓ in ♀)  
0.044 ml/kg - Hemoglobin (5% ↓ in ♂ and 6% ↓ in ♀), MCHC (4% ↓ in ♀)
6. Clinical Chemistry: 0.044 ml/kg - GPT (28 % ↑ in ♀). ALP (20 % ↑ in ♂)
7. Urinalysis: No significant changes
8. Organ weights: 0.033 ml/kg - Thyroid (29% ↑ in ♂)  
0.044 ml/kg - Spleen (16% ↑ in ♂ and ♀),
9. Necropsy: Slight hyperemia of the renal lymph nodes in some control and treated animals.

#### D. Mutagenicity Studies:

1. A mutagenicity study of hexafluoroisopropanol by use of microorganisms (Ames test). T. Mizuno, Central Research Laboratory, Maruishi Pharmaceutical Co., Study HFIP-7M1A; (1988a). HFIP in the presence and absence of S-9 mix did not induce reverse mutation in Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 and Escherichia coli strain WP 2uvr. The results indicated that although some bacterial strains demonstrated a slight increase in revertant colony formation, the increment ratio was found to be less than two. A dose-dependency was also not observed. Positive controls showed strong mutagenicity.

#### Summary of Toxicity and Mutagenicity Studies of Hexafluoroisopropanol (HFIP)

The acute inhalation estimated LC<sub>50</sub> values of hexafluoroisopropanol (the main metabolite of sevoflurane detected in urine) were 0.185% (0.178 - 0.189) and 0.184% (0.178 - 0.189) for male and female Slc Wistar rats, respectively. Comparing these LC<sub>50</sub> values with that of sevoflurane (=2.9%), HFIP is more toxic than the parent compound. Abdominal HFIP administration in Slc Wistar rats was associated with tissue adhesion and hepatic deformation, accretion and intussusception.

The intravenous LD<sub>50</sub> values for HFIP (specific gravity - 1.59) were 0.069 ml/kg in male and 0.017

ml/kg in female Wistar rats. No treatment related findings were observed at necropsy. The intensity of depressed locomotor movement, staggering gait or dysbasia was increased in a dose-related manner during seven days intravenous toxicity study of HFIP in Wistar rats. Mild anemia was observed in the males and females of 0.044 ml/kg group. Histopathological examination of the liver did not support the observed increase in GPT.

HFIP did not exhibit mutagenic activity in the presence or absence of S-9 in Ames test.

Toxicity Studies of Compound A:

1. Acute Toxicity of Compound A in Rats by One Hour Inhalation Administration.

Study No: CA-7A37; Tox-27, Vol. 2.3, pp 686-714.

Compound: Compound A,  $CF_2 = C(CF_3)OCH_2F$ , Lot No 1

Route: Inhalation, closed system, whole body exposure.

Dosage: Group: 1 2 3 4 5 6 7  
 %: 0, 0.070, 0.093, 0.107, 0.115, 0.122, 0.140  
 ppm: 0, 700, 930, 1070, 1150, 1220, 1400

Strain: Wistar (Slc;Wistar), 5 weeks old, 99-138 g body wt  
 Number: 6/sex/group  
 Control Treatment: Oxygen  
 Study Site: Central Research Lab., Maruishi Pharmaceutical Co.  
 2-2-18, Imazunaka, Tsurumi-ku, Osaka, Japan

Date: April 2, 1987-June 24, 1987

GLP/QAU Statements: The QAU statement was present.

The study includes daily observations, body weight determination, urinalysis at autopsy, blood chemistry (BUN, GOT, GPT, AP), and necropsy. All surviving animals were necropsied 14 days after administration. Dose levels were based on results from preliminary tests. A non-treated group was also in the study. The exposure time was 1 hour.

Results and Discussion

body wt: ♂ wt loss in all treated groups - up to 3 days in G5-6,  
 then wt gain  
 ♀ wt loss in G2-5, then wt gain

signs: locomotor movement ↓, bradypnea (≥ G3), loss of righting reflex (≥ G4), cyanosis, piloerection, lacrimation (≥ G3), diarrhea, backward movement, jumping, excitation, emaciation, convulsion prior to death, rigidity, tremor of extremities, emesis of foamy fluid, ocular hemorrhage - recovery of locomotor movement by

Day 2-  
 mortality: ♂ 2 G4, 5 G5, 6 G6, 6 G7, beginning D4 in G4 and ½ hour after inhalation in G7-  
 ♀ 6 G4, 3 G5, 6 G6, 6 G7, beginning 3 hours after

inhalation in G4 and 1 hour after inhalation in G7-  
 blood chemistry: 1 BUN in ♂ G2-3 ( $p < 0.01$ ) and 1 in ♀ G5 ( $p < 0.01$ )  
 urinalysis: occult blood, glucose, protein, and ketone bodies  
 observed mostly in animals that died - pH decreased

as dose increased-

gross pathology: (survivors) lymph nodes and thymus congestion, adrenal hypertrophy, fading/hypertrophy of kidney - lymph node congestion in non-treated and controls-

histopathology: slight/moderate coagulative necrosis of renal tubules or parenchymal cells of kidney, localized cell infiltration, erythrocyte in the medullary part of thymus, reactive proliferation of lymph node cells, and vacuolization of adrenals-

Congestion and hyperemia in the lungs were observed mainly at necropsy the day of death. Death was considered to be due to respiratory suppression in animals that died on the day of exposure and to renal impairment in deaths thereafter. In addition, rough kidney surfaces were seen in one or two dead animals in G5-6. Renal toxicity was also seen as slight to moderate coagulative necrosis of renal tubules or parenchymal cells. Proteinuria was also indicative of renal damage. The  $LC_{50}$  was 0.105% in females and 0.109% in males. The study considered Compound A to have high toxicity compared to Sevoflurane.

2. An Acute 3-Hour Inhalation Toxicity Study of Compound A and Compound A/Sevoflurane in the Rat via Nose-Only Exposure:

Report N<sup>o</sup>: 93-5162, Abbott Study N<sup>o</sup> TA93-423, Vols 2.9-2.12

Compound: Compound A, Lot N<sup>o</sup> 930906, 99.84% with BHT preservative;  
Sevoflurane, Lot N<sup>o</sup> 3426, purity not stated.

Formulation: Test materials in 40% oxygen/60% nitrogen.

Route: Nose only exposure.

Dosage:

Compound A: 0, 30, 61, 114, 202 ppm

Sevoflurane: 1.9, 2.5, 2.9%

Cpd A/Sevoflurane (ppm/%): 27/1.9, 35/1.7, 114/1.7, 265/1.8

Strain: Sprague-Dawley CD, 4-5 weeks old, mean group body wt  
♂ 182-284 g and ♀ 138-179 g

Number: 5, 15, or 20/sex/group

Control Treatment: 40% O<sub>2</sub>/60% N<sub>2</sub>

Study Site: Pharmaco LSR Inc., East Millstone, New Jersey

Date: November 11, 1993 - May 27, 1994

GLP/QAU Statements: Both present and signed.

There were 12 study groups. The minimum airflow rate was 10 L/min. The rats were observed daily through Day 15. Body weights were determined at several times during the study. Blood samples for hematology and blood chemistry parameters were collected immediately after exposure and 1, 4, and 14 days after exposure. Urinalysis was done on samples collected 1, 4, and 14 days after exposure. Plasma determinations of the two test compounds were done immediately after exposure and 1 day later. Interim sacrifices were done immediately after exposure and 1 and 4 days after exposure. All remaining animals were killed 14 days after exposure. Gross examination was done on all animals. Microscopic examination was evaluated on selected tissues from all animals except those killed immediately after exposure.

Results and Discussion

-signs: labored breathing (G4-12), decreased activity (G6-12)  
 during exposure - red nasal discharge during the first  
 week after exposure - signs mostly seen during  
 Sevoflurane and Compound A plus Sevoflurane exposure-  
 mortality: (from Vol. 2.9, p 3577)

Analytical Concentration*	Nominal Concentration		Mortality		Total		
	Cpd A (ppm)	Sevoflurane (%)	Cpd A (ppm)	Sevoflurane (%)		♂	♀
1	-	-	-	-	0/20	1/20	1/40
2	30	-	39	-	0/15	0/15	0/30
3	61	-	72	-	0/15	0/15	0/30
4	114	-	130	-	0/20	0/20	0/40
5	202	-	340	-	0/20	0/20	0/40
6	27	1.9	42	2.2	2/15	1/15	3/30
7	35	1.7	130	2.0	0/15	1/15	1/30
8	114	1.7	300	2.6	5/20	4/20	9/40
9	265	1.8	490	2.2	4/20	8/20	12/40
10	-	1.9	-	2.0	4/20	3/20	7/20
11	-	2.9	-	3.3	4/5	5/5	9/10
12	-	2.5	-	2.7	2/5	2/5	4/10

\* Cpd A and Sevoflurane concentrations were measured in G1-9 at 15-27,  
 75-86, and 135-147 minutes into the exposure. Concentrations of  
 Sevoflurane in G10-12 were measured 7-9 times during the exposure.

-body wt: no significant changes between G1-5 - significant ↓  
 in G6-9 vs G10 on day of exposure-

-hematology: various significant values, but they did not appear to be  
 of toxicological significance-

-blood chemistry: compared to G1

G4: Day 2 ♂ (↓ total protein (\*, 8%) and albumin (\*\*, 12%)-

G5: Day 1 ♂♀ ↓ Na<sup>+</sup>

Day 2 ♂ ↓ BUN (\*\*, 51%), ↓ creat (\*\*, 75%), ↓ total  
 protein (\*, 10%), ↓ albumin (\*\*, 12%) vs G1-

G8: Day 2 ♀ ↓ total protein (\*, 9%) vs G10-

G9: Day 1 ♂ ↓ AP (32%), ↓ BUN (\*\*, 2.4x), ↓ creat (\*\*, 50%)-

Day 2 ♂ ↓ creat (\*, 3.7x), ♀ ↓ total protein (\*\*, 17%),  
 ♀ ↓ albumin (\*\*, 16%)-

-urinalysis: G4 ketones and occult blood D2 and D5-

G5 ketones, occult blood D2 and D5, glucose,  
 protein, and NAG/creatinine D2 only-

G8 ketones and occult blood D2 and D5-

G9 ketones and occult blood D2 and D5-  
 glucose, protein, N-acetylglucosamidase(NAG)/  
 creatinine D2 only-

-necropsy: similar findings in controls and treated groups-

heart: acute/subacute inflammation ♂ G1(0%), G2(50%),  
 G3,6,7(10%), G4,12(6.7%), G5,9(13.3%), G8(6.3%)-  
 ♀ G1,5(6.6%), G2(10%), G4(13.3%)-

kidney: discolored foci, discolored areas, dilatation-  
 lungs: fluid filled, discolored, discolored foci, firm,  
 hemorrhage-  
 submandib/max lymph node: discolored, enlarged-  
 liver: discolored areas-  
 u. bladder: distended, discolored-

**-histopathology:**

heart: acute/subacute inflammation

kidney: tubular necrosis and epithelial hyperplasia G4  
 (114 ppm, minimal/slight, 10/15♂, 2/15♀), G5 (202 ppm,  
 slight/moderate, 12/15♂, 12/15♀), and G6, more severe  
 in G8 and G9, most severe D2, least severe D15, higher  
 incidence and severity in ♂-  
 mineralization G3-9,12-  
 inflammation in all drug groups, higher in G4, 5, 7,  
 8, 9, 11-

nasal turbinates:

olfactory epithelium: degeneration and desquamation,  
 significant in G5, appeared to be lessened in presence  
 of Sevoflurane-  
 eosinophilic droplets-  
 subepithelial mineralization: G5,8,9,12-  
 bone: endosteal osteoclast hyperplasia: G5,6,8,9,12-

Compound A alone did not produce any premature mortality at the highest dose (202 ppm). Blood chemistry increases occurred in BUN and creatinine, with decreases in total protein and albumin at 202 ppm. Urinalysis revealed ketones, occult blood, glucose, protein, and an increased NAG/creatinine ratio at 202 ppm. Microscopic findings were limited to the kidney (tubular necrosis, epithelial hyperplasia, and mineralization) and nasal turbinates (degeneration and desquamation). It appeared that subacute/acute inflammation was more prevalent in the heart, although inflammation was seen in most all groups.

Mortality occurred in all combination groups containing Sevoflurane and in those groups exposed to Sevoflurane alone. Labored breathing and decreased activity were seen in these groups. AP, BUN, and creatinine increased and total protein and albumin decreased. Renal findings were similar to what was observed in the Compound A exposed animals but were more severe in Groups 8 and 9.

3. Acute Toxicity of Compound A in Rats by 3 Hour Inhalation Administration:

Study N<sup>o</sup>: CA-8A37, Vol 2.3, pp 858-899.

Compound: Compound A, CF<sub>2</sub>=C(CF<sub>3</sub>)OCH<sub>2</sub>F, lot N<sup>o</sup> 8303

Formulation: Liquid, used as is.

Route: Inhalation in a closed system - generated CO<sub>2</sub> removed.

Dose Levels: Group:	1	2	3	4	5	6
Concn. (%) ♂:	0	0.017	0.011	0.025	0.035	0.049
♀:	0	omitted	0.011	0.029	0.034	0.046

Strain: Slc:Wistar, 5 weeks old, body wt (g): ♂ 110-124, ♀ 96-111

Number: 6/sex/group  
Control Treatment: Oxygen  
Study Site: Central Research Lab., Maruishi Pharmaceutical Co.  
2-2-18 Imazu-naka, Tsurumi-ku, Osaka, Japan  
Date: May 11, 1988 - June 28, 1988  
GLP/QAU Statement: Both present but not signed.

Dosage was based on a preliminary study in  $\sigma$  rats in which 6/6 died at concentrations between 0.067% and 0.300%, 2/6 died at 0.045%, and no deaths occurred at 0.030%.

The dosages are the observed concentrations of Compound A in the 25 L chambers housing the six males or females per group. The animals were observed daily. Clinical signs were recorded. Body weights were determined Days 1, 2, 3, 5, 7, 10, and 14. Urinalysis was done at necropsy when collection was feasible. Necropsy was done on all dead animals and on survivors on Day 14. Histopathology was conducted on the livers and kidneys of 1 male and 1 female of G5 and 2 males and 3 females of G6.

#### Results and Discussion

- deaths:  $\sigma$  1/6 G5 ½ hour after dosing  
 $\sigma$  6/6 G6 during dosing  
 $\text{?}$  2/6 G5 4 days after dosing  
 $\text{?}$  6/6 G6 during and up to 1 hour after dosing
- signs: nictitation, ptosis, inhibition of locomotor movement, prone position, slight bradypnea, cyanosis, tremor, piloerection, nasal hemorrhage, chromodacryorrhea, tonic convulsions in animals dying - signs in most drug groups-
- body wt: 1 in  $\sigma$ G5 and  $\text{?}$ G4, in some animals up to D5
- urinalysis: proteinuria in G1-6, glucosuria and ketone bodies only in dead animals, occult blood in survivors and animals dying, no urobilinogen and bilirubin in any animal-
- necropsy: terminal kill
  - lungs: congestion in all groups-
  - kidney: faded color G4-5
  - uterus: retention of fluid 1 G4
  - l. nodes: hyperemia
  - thymus: hyperemia
  - pancreas: hyperemia
- necropsy: animals that died
  - lungs: congestion, hyperemia, or hemorrhage in all
  - kidneys: faded color
  - testis: undescended 1 G6
- histopathology:
  - kidney: moderate acute tubular necrosis in 1  $\sigma$  and 1  $\text{?}$  (G67)
  - Lungs: moderate pulmonary congestion 1  $\sigma$ / $\text{?}$  G6

The results of this study were similar to what has been observed in the previous study. The calculated  $LC_{50}$  in this study is in the range of 340 to 490 ppm. Exposure to 460-490 ppm was lethal to all animals. The lungs (moderate congestion) and kidneys (tubular necrosis) were the major

target organs. There were no significant differences in the toxicity between sexes.

4. Toxicity of Compound A in Rats: Effect of a 3-Hour Administration C. T. Gonsowski, et al. Anesthesiology 80, No. 3, 556-565 (1994). Vol 2, 2, pp 454-463.

Male Wistar rats (10/group), five to six weeks old, with an average weight per group of 124-159 g were exposed (whole body) three hours to 0, 25, 50, 100, 200, 300, 350, and 400 ppm (2 groups) of Compound A,  $\text{CF}_2 = \text{C}(\text{CF}_3)\text{OCH}_2\text{F}$ , in oxygen. The animals were killed on Day 1 or Day 4, and brains, kidneys, lungs, livers, and the small intestines were examined with the light microscope.

No deaths occurred during the exposure; however, one death occurred Day 3 at 300 ppm, eight deaths occurred between Day 1 and Day 4 at 350 ppm, and all rats died prior to Day 4 at 400 ppm. The  $\text{LC}_{50}$  was estimated to be  $331 \pm 13$  ppm. Exposure levels  $\geq 100$  ppm were irritating to the eyes, producing tears. Convulsive activity, such as rigid extension of the hind limbs and clonic movements of the forelimbs, occurred during and after exposure to  $\geq 350$  ppm. Trembling was also reported. No animals appeared to be anesthetized. A dose related body weight gain reduction became significant ( $p < 0.01$ ) at  $\geq 100$  ppm.

Brain lesions (small pyknotic neuronal nuclei with eosinophilic cytoplasm) were seen at  $\geq 350$  ppm (10%) and 400 ppm (15%). These lesions were seen in rats with and without convulsive activity. Periportal fatty infiltration, hepatic cellular swelling, and occasional pyknotic hepatocyte nuclei were seen at 300 ppm (5%), 350 ppm (30%), and 400 ppm (10%). The most damage was seen in the corticomedullary junction of the kidney of rats exposed to  $\geq 50$  ppm (30%), consisting of swelling and/or necrosis of tubular cells extending into the cortex. These lesions were dose related and occurred in 75-100% of the animals in the higher exposed groups. The lungs and duodenum showed no histologic changes.

The authors state the concentration of Compound A can go up to 61 ppm in clinical practice. This would be in the range where kidney damage was observed in these rats.

5. Toxicity of Compound A in Rats: Effect of Increasing Duration of Administration. C. T. Gonsowski, et al. Anesthesiology 80, No. 3, 566-573 1994. Vol 2, 2, pp 464-471.

In these studies Wistar rats (10  $\sigma$ /group) were whole body exposed to 0, 12.5, 25, 50, 75, 100, 125, 150, 175, 200, 225, and 250 ppm of Compound A for six or 12 hours. Surviving rats were killed on Day 1 or Day 4. Brains, kidneys, lungs, livers, and small intestines were examined with the light microscope. The average body weight ranged from 130 to 191 g per group.

A 6 hour exposure at  $\geq 200$  ppm or 12 hour exposure at  $\geq 100$  ppm resulted in a significant ( $p < 0.01$ ) weight loss. No deaths occurred during the exposure periods and none of the animals appeared to be anesthetized. Mortality did occur at  $\geq 175$  ppm in the 6 hour exposure and one death occurred at 100 ppm in the 12 hour exposure. The  $\text{LC}_{50} = 203 \pm 4$  ppm for the 6 hour study and  $\text{LC}_{50} = 127 \pm 9$  ppm for the 12 hour study. Eye irritation with tearing was evident at  $\geq 100$  ppm. Pulmonary congestion and/or edema was seen in 18/50 rats exposed to 175-250 for 6 hours and killed Day 4; however, there was no difference in the 12 hour exposed rats killed Day 1 or Day 4. Kidney corticomedullary tubular toxicity occurred at  $\geq 50$  ppm and was more severe in rats killed at Day 4. Dose related injury was also reported in the renal cortex. The threshold for renal injury

Request "5. "It is recommended that weight in grams be included in the Stability Report for Sevoflurane Assay results. The percentage values can be parenthesized."

Response: The sevoflurane purity data presented in the Stability Report are on a % w/w basis. This is consistent with the specifications of all the other compendial inhalation anesthetics currently on the market, such as isoflurane, enflurane, and halothane etc.

The purity of sevoflurane presented in the Stability Report was obtained by subtracting from 100% the total impurity found in the product. The sevoflurane purity of the stability samples reported are all at 99.99% purity, which is equivalent to 0.9999 g/g. Therefore, the purity of sevoflurane in weight per gram in all the stability data will be 0.9999 g/g.

Therefore, based on the accepted compendial data presentation i.e. (%) and the established purity of the drug product, we feel that the purity value expressed solely in % is acceptable.

COMMENT:

Response is acceptable.

Request "6. It is noted in the labeling section under Dosage and Administration the statement, "Surgical levels of anesthesia are usually within concentration of 0.5 - 3% sevoflurane with or without the concomitant use of nitrous oxide ..." In terms of grams, how much Sevoflurane are we talking about?"

Response: The concentration of sevoflurane used in the anesthetic circuit refers to the volume/volume basis in the vapor phase. A sevoflurane concentration of 0.5% to 3% (v/v) in the vapor phase is equivalent to 4.1 to 24.5 gram of sevoflurane per 100 Liters of gas. An example of the calculation is shown below to indicate the amount of sevoflurane required to generate the desired concentration of sevoflurane in the vapor phase. Please note that the volume percent of sevoflurane in the anesthetic circuit is controlled by a sevoflurane agent-specific vaporizer. The vaporizer is calibrated by the manufacturer to deliver the required amount of sevoflurane to the circuit.

0.5% (v/v) = 0.5 Liters sevoflurane per 100 Liters of gas

At 25°C the volume of 1 mole of sevoflurane gas is 24.47 L (using gas law  $PV=nRT$ ). The molecular weight of sevoflurane is 200 g/mole. Therefore 0.5L of sevoflurane in gas phase is equal to 4.1 gram of Sevoflurane

$$\frac{0.5 \text{ L}}{24.47 \text{ L/mole}} \times 200 \text{ g/mole} = 4.1 \text{ g}$$

3% = 3 liters sevoflurane per 100 liters of gas

$$\frac{3 \text{ L}}{24.47 \text{ L/mole}} \times 200 \text{ g/mole} = 24.5 \text{ g}$$

COMMENT: Response is acceptable.

Request 7. With the concerns about Compound A in particular, submit a listing of its physical and chemical values. Include the same information for any of the other impurities."

Response: This information is included in our presubmission page 186 - 189 (See Attachment 3) The information submitted is as follows:  
Compound A-

Comment: Response somewhat acceptable.

Request Please send me a copy of each of the attached chromatograms with legible retention times shown and peaks identified ...."

Response: Appended in Attachment 4 are the requested chromatographs for Figure 23, 26, 27 which were included in the CMC presubmission.

COMMENT: Legible chromatograms were submitted.

AMENDMENT : Jan 5,1995

1. Submit a Certificate of Analysis of your reference standard showing its quality as compared to the testing of Sevoflurane in the Table below.

Table IV Specifications for Sevoflurane		
Test	STM#	Specifications
<hr/>		

Response:

The firm submitted the table shown below;

Certificate of Analysis of Reference Standard Lot # 210151			
Test	STW	Specifications	Results

COMMENT:

In comparing some of the results of the reference standard testing with those of six production lots, shown in the table below, at the end of six months, their values are very close to those of the reference standard and in some instances the results better.

Table XXXX Stability Data (continued) 250 mL Screw Cap Closure System (Reclaim Product)								
Test Performed	Fluoride	Acidity** or Alkalinity	Non- volatile Residues	Water Content	Total Imp. wts Cpt. A	Cpt. A	Other Largest Imp.	Seve Purity
/								

View Method Attachment

b

Request: 2. On pages 239-244, data was submitted for 36 lots of bulk drug manufactured tested as per current test batch methods.

Batches:

#C-1, 2, 3, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 23, 24, 25, 26, 27, 28

#71104, #00210, #11224, #1120061

- "a) Clarify the absence of such information as:
- Date these batches were manufactured
  - Date these batches were tested
  - Explain the batch numbering system.
- "b) For all the above batches clarify the absence of the following data:
- Refractive Index
  - Identification (IR) include copies of spectra
  - Fluoride Ions
  - Largest Single Impurity
  - Acidity/Alkalinity - the word "Pass" is not acceptable, include actual data.
- "c) Include the chemical names of Compound A, Largest Single Impurity and any of the known Total Impurities in your Tables.
- "d) On pages 239 to 243, some of the values for Largest Total Impurities are out of specification limits. Please explain."

Response:

2. a.) Firm submitted a table showing the dates the batches were manufactured and tested. ( Date range: 10/3/83 - 3/24/86

Response: continued: 1. a.)

Firm explained the batch numbering system as follows:

1st digit = the last digit of the year in which the bulk drug was filled.  
Next two digits = the month in which the bulk drug was filled.  
Next two digits = the day in which the bulk drug was filled.  
Last two digits are used if the lot represents a routine continuous filling operation. (i.e. 01-09), or pooled tailings from various routine filling operations (i.e., 10-15).

For example: Lot 211231 represents a lot filled in 1992, in November, on the 23rd day of November, and is a routine continuously filled lot (i.e., not a lot including pooled tailings from other lots of bulk drug).

Lot numbers containing only five digits represent the same lot numbering scheme, without identification of filling method. The latest lot numbering scheme that is currently standard practice is as described above, with a zero preceding all single digit numbers used to describe the filling method.

COMMENT: Response acceptable.

- 2 b.) At the time these lots were produced, the bulk drug specification did not require such testing. However, when Abbott Laboratories took over the developmental program for sevoflurane these specifications were included.
- 2c.) The firm included the names of "ALL" potential impurities for Sevoflurane. However, my question was to report the chemical name of Compound A on all Tables and identify the single largest impurity in all of their tables.

I will call this to the firms attention , when they submit future Tables.

- 2 d.) The firm indicated that the lots on pages 239-243 were out of specification limits for the largest single impurity, but when Abbott took over and refined the method; the data fell within acceptable limits.

Responses to question #2 are acceptable.

Request #3. In regard to the filling process, what in-process controls are applied to assure that the air used to blow-out empty 250 mL bottles is acceptable and what in-process controls are applied to assure that the bulk drug prior to filling is properly filtered. Identify the particles or organism that may be present.

What evidence do you have that this product does not support growth? We call your attention to the fact that the agency is in the process of writing regulations that require liquid anesthetics to be sterile."

Response:

The firm indicated that the Pharmacopoeia specified microbial inhibition test with the required types and concentrations of bacterial and fungi and the results indicated that sevoflurane met these requirements for classification as a microbial inhibition agent.....etc.

It should be noted that this drug is not directly administered in liquid form to patients. Only the volatile vapors of sevoflurane are administered to patients.

Response:

Firm should be requested to submit the evidence that shows Sevoflurane met the requirements to be classified as a microbial inhibition agent.

The response to the filtering is acceptable.

Request: "4. It is noted in the Table below, that at the end of six months "ALL" of the lots are reading much below the specification limits. Explain how your specification limits were derived and show the quality of your product at both extreme ranges for all tests indicated."

Table XXXXI Stability Data (continued) 250 mL Screw Cap Closure System (Reclaim Product)								
Test Performed:	Fluoride	Acidity** or Alkalinity	Non- volatile Residues	Water Content	Total Imp. w/o Cpd. A	Cpd. A	Other Largest Imp.	Sevo Purity
Test Method Assignment:								
Final Specifications:								
Lot # / Stability #	Temp	Month Position						

Response:

The firm indicated that their specification limits are based on data from 36 developmental lots. The Table below gives average high and low values from testing these lots

The following table lists the specification ranges verified for the 36 developmental lots for the key volatile analogues included in the established bulk drug specification:

TEST	SPECIFICATION	LOW	HIGH
------	---------------	-----	------

COMMENT: Response acceptable for the present time.

Request: \*5. Clarify the revised specification in your stability protocol for Compound A in Appendix J, page 492 of

Response:

Firm indicates that the specification was incorrect and it should have read in the liquid product and this value is consistent with the levels present in the current manufacturing process.

Question:

1. Describe the assay and purification tests performed on the assay test and free acid test performed on calculations and appropriate graphs or chromatograms.

and  
include actual

Response:

following page.

## COMMENT:

The firm submitted a chromatogram, showing the retention area of the proposed impurities, namely

B.) Assay and Free Acid test fo

C.) Free Acid Test: Performed by

Question:

2. Submit the actual supplier/manufacture's Certificate of Analysis for  
(English Translation)

Response:

2. Quality control unit performs the analysis of raw material, but the control unit does not submit the Certificate of Analysis of . It submits Test Record as shown at attached translated document with IR chart.

2. Comment:

The DMF holder has indicated that the source of is and upon receiving the substance they perform the following in-house testing:

DMF 11, pages 63 and 149- additional information.

Question:

3. In regard to recovered describe the assay test and submit actual calculations and appropriate chromatograms or graphs.

Response:

## 3. Comment:

The firm submitted a description of the analytical methods and the actual formulas used for calculations. DMF , pages 10-14- additional information

Question:

4. On page 82, in regard to the following statement,

"A fully characterized and analyzed lot of Sevoflurane will be kept under controlled conditions as a reference standard."

Submit the Certificate of Analysis for your reference standard of Sevoflurane.

Response:

4. A sample of certificate of analysis of reference standard (Lot 404011) is shown on page 26:

## 4. Comment:

A Certificate of Analysis was submitted for the reference standard. See the following page.

page

PURGED

was 25-50 ppm, with the lower value for the long exposure. No injury was found in the duodenum, cerebrum, or liver of rats exposed to 250 ppm.

These authors expressed some concern that the safety ratio was less than 8 when Sevoflurane is administered using low flow rates of background gas.

6. Subacute toxicity of compound A on 28 alternate days in rats by inhalation. Y. Kawai, Central Research Laboratory, Maruishi Pharmaceutical Co., Ltd., Study CA-8S37; (1989). Seventy-five male and seventy-five female six-week old Sic:Wistar rats (135 - 159 g males and 105 - 123 g females) were divided into five groups. Five animals from each group were assigned to the five recovery groups. Fifteen animals at a time were placed in a 120 liter chamber filled with pure oxygen. Oxygen flow was kept at 5 l/min by an air pump. Compound A at a volume corresponding to the specified concentration (0.003, 0.006 and 0.012%) was added dropwise to the inside of the chamber and distributed uniformly. Ten liters of 60 mm barium hydroxide was incorporated in the closed system to eliminate the carbon dioxide gas included in the expired gas. Exposures were carried out on 28 alternate days for three hours a day three times per week (Monday, Wednesday and Friday). The animals were kept under observation during the exposure period and two week recovery period after the final exposure.

#### Measurements and Observations:

General appearance, viability, clinical signs	Daily, during inhalation and 2 hours after inhalation
Bodyweight	Three times a week
Food consumption	Weekly
Ophthalmology	Before inhalation and autopsy
Urinalysis	Week 7, end of inhalation and recovery periods
Autopsy, organ weight and Necropsy	End of inhalation and recovery periods

#### Results:

- Clinical Observations: No differences (soft stool, diarrhea)
- Mortality: None
- Body weight: 0.012% - Decreased in females
- Food and water consumption: No difference
- Ophthalmology: No abnormalities in cornea, iris and fundus of all animals.
- Hematology: 0.003% - MCV (2% ↓ in ♂), 0.012% - MCV (4% ↓ in ♀)
- Serum Chemistry: No differences
- Urinalysis: No change
- Organ weight: At the end of inhalation.
  - 0.003% - Absolute and relative weights of kidney (4% ↓ in ♂)
  - 0.006% - Relative kidney weight (7% ↓ in ♂)
  - 0.012% - Absolute and relative weights of kidney (12% ↓ in ♂ & ♀), increased relative weights of brain (1%), heart (13%), lung (8%), thyroid (25%) and adrenal (11%) in females.
- After the recovery period: No change
- Autopsy: Control - Redness in thymus (1♂) lung congestion (1♂ & 2♀), liver nodules (1♀ & 1♂)
  - 0.003% - Lung congestion (1 ♀)
  - 0.006% - Lung congestion (2 ♀), kidney fading (1♂)
- Histopathology: After inhalation.

Control - Thyroid ultimobranchial body (1♂ & 1♀), liver microgranuloma (3 ♂ & 2♀), kidney tubules (1♀)

0.003 - kidney tubules (1♀)

0.012 Thyroid ultimobranchial body (1♂ & 1♀), liver microgranuloma (3 ♂ & 2♀), kidney tubules (2♂)

After recovery period. No dose-related changes

12. Pharmacokinetics: Not determined.

7. Reaction of Sevoflurane and its Degradation Products with Soda Lime: M. Morio, et al. Anesthesiology 77,1155-1164, 1992. Vol 2,3, pp 715-724.

These authors studied the acute and chronic toxicity of Compound A ( $\text{CF}_2 = \text{C}(\text{CF}_3)\text{OCH}_2\text{F}$ ) and Compound B,  $\text{CH}_3\text{OCF}_2\text{CH}(\text{CF}_3)\text{OCH}_2\text{F}$ , two degradation products of sevoflurane. The purity of Compounds A and B were 99.0%-99.9% and 98.8%-99.6%, respectively. Both compounds were evaluated in the Ames test. Compound A was also evaluated in a chromosome aberration test with mammalian cells in culture.

Male and female 5 week old Wistar rats (Slc:Wistar) were exposed 1 hour to 700, 930, 1070, 1150, 1220, and 1400 ppm of Compound A in an atmosphere of oxygen. A 3 hour exposure to male(female) at 110(160), 250(290), 350(340), and 490(460) ppm was also evaluated. In the chronic part of the study, male and female rats were exposed to 30, 60, and 120 ppm of Compound A for 3 hr/day 3 days/week for 8 weeks. A 3 hour exposure with Compound B was evaluated in male(female) rats at 800(400), 1500(1200), and 2300(2500) ppm.

One Hour Exposure to Compound A:

Toxic signs were decreased locomotor activity, prone position, loss of righting reflex, bradypnea, cyanosis, lacrimation, and piloerection. Deaths occurred from 30 min to 9 days after exposure. The  $\text{LC}_{50}$  was 1,090 ppm in males and 1,050 ppm in females. Lung congestion and hyperemia were seen in animals that died on exposure day. Kidneys were discolored and had rough surfaces. BUN increased ( $p < 0.01$ , 31%) in 3/6 females that survived at 1,150 ppm. Occult blood, sugar, protein, and ketone bodies were observed in the urine of dead rats. The only histopathologic findings were degeneration and necrosis of renal tubules in dead animals and slight necroses in those that survived one day after exposure.

Three Hour Exposure to Compound A:

Toxic sign were similar to those observed in the one hour exposure. Deaths occurred at > 250(290) ppm - 12/12 died during exposure at 490(460) ppm and 3/12 died by Day 4 at 350(340) ppm. Congestion, hyperemia, and hemorrhage was seen in the lungs of animals that died on the day of exposure, and degeneration and necrosis of renal tubules occurred in animals that died four days after exposure. No other lesions were reported. The  $\text{LC}_{50}$  was 420 ppm in males and 400 ppm in females.

Chronic Exposure to Compound A:

The body weight of females that were exposed to 120 ppm was significantly less ( $p < 0.01$ ) on Day 8. No histopathologic changes were said to relate to Compound A at any exposure level.

Three Hour Exposure to Compound B:

No deaths occurred. The toxic signs were staggering gait, decreased locomotor activity, slight bradypnea, and prone position. No changes were found in the urine or at necropsy.

**Mutagenicity Tests:**

Compound A was negative in the reverse (Ames) test in the absence of S9 (up to 625 µg) or in the presence of S9 (up to 1,250 µg) in 4 strains of *S. typhimurium*. It was also negative in 1 strain of *E. coli*. Exposure of fibroblasts to 7,500 ppm of Compound A for 1 hour did not induce chromosome aberrations. The micronucleus test with Compound A was also negative. In the Ames test Compound B was negative up to 1,250 µg.

8. Dose Dependent Degradation of Sevoflurane to Compound A. Foden et al. Anesthesiology Vol 81, No 3A, Sept 1994, ASA Abstracts A432.

The degradation of Sevoflurane to Compound A in the presence of soda lime was shown to increase with time and reach a plateau after 2 hours. The mean plateau concentrations of Compound A increased linearly over the 1%, 2%, and 4% concentrations of Sevoflurane that were studied. Canister temperatures were higher at the gas flow inlet and decreased toward the outlet, with temperatures approaching a plateau by 90-120 minutes for the three concentrations of Sevoflurane.

9. Sevoflurane Degradation in a Circle System at two Different Fresh Gas Flow Rates. J.T. Munday, et al. Anesthesiology Vol 81, No 3A, Sept 1994, ASA Abstracts, A433.

The authors measured peak Compound A concentrations in 31 surgery patients (surgery duration > 1 hour). The patients lungs were ventilated with Sevoflurane in N<sub>2</sub>O/O<sub>2</sub>, using a circle system and soda lime as the CO<sub>2</sub> absorbent. Fresh gas flows (FGF) were 0.5 or 2.0 L/min. The end-tidal sevoflurane concentrations were between 1.7% and 2.2%. Soda lime temperatures were 41.5°C-41.6°C. The results follow:

Peak Compound A concentrations (ppm)						
EGE	N		Mean	SD	Min	MAX
0.5	16	insp	19	6.3	12	32
		expir	13	5.0	8	26
2.0	15	insp	17	4.9	10	25
		expir	11	3.1	7	18

Compound A concentrations are claimed to be significantly different between the two arms at both fresh gas flow rates. It is also noted that the slower gas flow results in a higher concentration of Compound A in both the inspiration and expiration arms of the system.

10. Ames metabolic Activity Test to Assess The Potential Mutagenic Effect of I-654 (Compound A): Vol 2,3, pp 774-791.

Compound: I-654 (Compound A), batch N° 3776-37, purity 99.9% by GC

Dose Levels: Range finding test: 5, 50, 500, 5000 µg/plate

Mutation test: 14, 50, 150, 500, 1500 µg/plate

• Strain: TA 1535, TA 1537, TA 1538, TA 98, TA 100

Number: 3 plates/strain/dose level

Positive Control:

(+)S9: 2-aminoanthracene (2 µg/plate): TA 1535 and TA 1537

2-aminoanthracene (0.5 µg/plate): TA 1538, TA 98, TA 100

(-)S9: 2-Nitrofluorene (2 µg/plate): TA 1538

2-Nitrofluorene (1 µg/plate): TA 98

9-Aminoacridine (80 µg/plate): TA 1537

N-ethyl-N'-nitrosoguanidine (5 µg/plate): TA 1535

N-ethyl-N'-nitrosoguanidine (3 µg/plate): TA 100

Study Site: Huntingdon Research Centre, Huntingdon England

Date: October 30, 1986 to November 9, 1986

GLP/QAU Statements: Both present and signed.

Compound A (I-654) was toxic at 5000 µg/plate to all of the strains. Under the conditions of the study, the colony counts were not increased twofold above the solvent controls in any of the tester strains, nor was there a statistically significant dose-related increase in the number of revertant colonies, either in the presence or absence of rat derived S9.

#### 11. Chromosome Aberration Test of Compound A With Mammalian Cells in Culture:

Study N°: CA-7M1A, Vol 5, pp 1530-1547.

Compound: Compound A, Lot N° 1

Route: In vitro cell culture

Dose Levels: 15, 1500, 7500 ppm v/v Compound A

Strain: Chinese hamster fibroblast cells (passage level 15)

Number:  $1.2 \times 10^4$  cells/plate, 2 plates/exposure repeated twice

Control Treatment: (-) control - Cell culture treated with air.

(+) control MNNG, 1.40 µg/ml

Study Site: Central Research Laboratory, Maruishi Pharmaceutical

Co., Ltd., 2-2-18 Imazu-Naka, Tsurumi-ku Osaka

Date: May 30, 1987 to May 17, 1988

GLP/QAU: Statements: Both present but no signatures.

Cells were exposed to Compound A in a 10 L chamber for 1 or 2 days and counted. Since Compound A is not water soluble, the study was not conducted with drug metabolizing enzymes (S9). The plates were incubated in a 5% CO<sub>2</sub> atmosphere at 37°. The cells were exposed 60 minutes to the Compound A concentration after the chambers became homogenous. The plates were covered but contained a space to allow ventilation. The medium is known to change color, using a CO<sub>2</sub> pH indicator, hence it was assumed the cells were exposed to Compound A vapor, as the color changed. At 24 and 48 hours after exposure, one hundred metaphase chromosomes were examined from each plate.

### Results and Discussion

The average observed concentration for the 3 concentrations in each of the 2 studies were 14.4 and 15.5, 1390 and 1380, and 7680 and 7660 ppm. There were no differences in the 24 or 48 hour cell exposure to Compound A. The structural aberration frequency for the air exposure was 0% compared with 0.5 and 1.5%, 0.5 and 2.5%, and 1.0 and 2.5% for the low, mid, and high exposure at 24 and 48 hours. The positive control value was 28.5% and 43.5% for the 24 and 48 hour exposure, respectively. The results indicate Compound A does not induce chromosomal aberrations in Chinese fibroblast cells under the conditions in which the study was conducted.

Even though the compound is water insoluble, some of the drug was incorporated into the cell culture, as some aberrations occurred. Therefore the study should have been done with S9. The amount of actual cell exposure (uptake) remains unknown in this type of study. This study, therefore, may not be a valid evaluation of the chromosomal aberration potential of Compound A.

#### 12. Evaluation of Compound A for Active Systemic Anaphylaxis in Guinea Pigs: Report N° R&D/93/748 - Study N° TF93-418: Vol 2.3, pp 545-576.

The potential of Compound A to produce systemic anaphylactic reactions was evaluated in male Cri:IAF(HA)BR six week old hairless guinea pigs weighing 250-350 g. Abbot Laboratories conducted the study. A QAU statement was present and signed. The test was set up as follows (from Vol. 3, p 570):

Test Group	N° of Animals	<u>Test Material (mg/Animal/Dose)</u>	
		Sensitization (IP) <sup>a</sup>	Challenge (IV) <sup>a</sup>
T <sub>0</sub>	6	Vehicle <sup>b</sup> (0)	Compound A <sup>c</sup> (1)
T <sub>1</sub>	6	Compound A <sup>c</sup> (1)	Compound A <sup>c</sup> (1)
T <sub>2</sub>	6	- <sup>d</sup>	Compound A <sup>c</sup> (1)
T <sub>3</sub>	6	Egg Albumin <sup>e</sup> (1)	Egg Albumin <sup>e</sup> (1)

<sup>a</sup> IP = intraperitoneal; IV = intravenous

<sup>b</sup> Vehicle = DMSO: 0.9% NaCl for injection, USP (1:4, v/v), DMSO was found to be the best vehicle for diluting Compound A. This concentration was found to be non-irritating when injected IP in preliminary testing.

<sup>c</sup> 0.1% (v/v) Compound A in vehicle.

<sup>d</sup> Animals will not be treated during sensitization.

<sup>e</sup> 0.1% egg albumin in 0.9% NaCl for injection, USP.

The sensitization injections (1 ml/animal) were made three times/week until each animal had received a total of six injections. Animals were challenged with Compound A (1 ml/animal) or egg albumin (1 ml/animal) two weeks after the last IP injection.

A bluish discoloration of the legs or feet occurred in one animal in T<sub>0</sub> and one animal in T<sub>1</sub>. Other clinical signs were not seen after 24 hours following challenge. Dyspnea and ataxia occurred in all animals of T<sub>3</sub> after iv challenge with egg albumin, with convulsions and death occurring in 2/6 of these animals.

Compound A did not produce systemic anaphylaxis under the conditions of this study.

### Summary of Toxicity Studies of Compound A

The LC<sub>50</sub> value in Wistar rats exposed one hour was 1090 ppm in males and 1050 ppm in females. LC<sub>50</sub> values in 3 hour exposure in Wistar rats were 350-490 ppm in males and 340-460 in females. In on other 3 hour exposure study in male Wistar rats, the estimated the LC<sub>50</sub> value was 331 ± 13 ppm. The calculated 3 hour value reported by Morio, et al. [Anesthesiology 77, 1155 - 1164, 1992] in Wistar rats was 420 ppm in males and 400 ppm in females. A 3 hour exposure study in male and female Sprague-Dawley rats resulted in no mortality at 202 ppm, the highest exposure used in the study. Six and 12 hour exposures in Wistar rats resulted in LC<sub>50</sub> values of 203 ± 4 ppm in males and 127 ± 9 ppm in females. Compound A appears to be equally toxic to males and females. Respiratory suppression was considered the cause of death in animals that died on the day of exposure and renal toxicity the cause of death in animals that died thereafter.

Clinical signs were eye irritation, reduced locomotor movement, bradypnea and labored breathing, loss of the righting reflex, cyanosis, and convulsions prior to death. Serum chemistry parameters that were significantly changes were increases in BUN and creatinine, and decreases in total protein and albumin. The urine tested positive for ketones, occult blood, glucose, and protein.

Renal tubular necrosis and epithelial hyperplasia of renal tubules was a common finding in all of these studies and was reported at ≥ 50 ppm. Pulmonary congestion was also reported. Degeneration and desquamation of the olfactory epithelium in the nasal turbinates was seen in rats that were exposed (nose-only) to 202 ppm for 3 hours. Small pyknotic neuronal nuclei with eosinophilic cytoplasm in the brain were reported in animals dosed at ≥ 350 ppm; however, this was suggested as being due to hypoxia. Hepatic injury was reported in rats exposed to 300 ppm.

Compound A was negative in the Ames test with 5 strains of *S. typhimurium* in the presence or absence of S9 and negative in 1 strain of *E. coli*. The chromosome aberration test with mammalian cells in culture was also negative.

### Toxicity Studies of Compound B

#### Acute Inhalational Study:

1. Acute toxicity of compound B in rats by three hours inhalational administration. Y. Kawai, Central Research Laboratory, Maruishi Pharmaceutical Co., Ltd., Study CB-8A37; (1988b). Six:Wistar rats of 5 weeks old weighing 106-118 g in males and 93-103 g in females were divided into 4 groups consisting of 6 rats each. Animals were placed in a close system filled with pure oxygen containing barium hydroxide to eliminate carbon dioxide. Although the animals were exposed to 0.2, 0.4 and 0.8% of compound B for three hours, the observed concentrations are given on the next page.

Expected concentration (%)	Sex	Observed concentration (%)	Maximum evaporator time (min)	Maximum concentration (%)
0.2	M	0.08	20	0.143
0.2	F	0.04	10	0.087
0.4	M	0.15	20	0.256
0.4	F	0.12	20	0.244
0.8	M	0.23	20	0.330
0.8	F	0.25	20	0.388

**Results:****Mortality:** None**Body weight:** No difference**General Signs:** Staggering gait, depressed locomotor movement and respiratory rate, dysbasia and prone position in all treated animals,**Urinalysis:** 0.2% (0.08%) - Occult blood (1♀), urobilinogen (2♂, 1♀), bilirubin (1♂)

0.4% (0.14%) - Occult blood (1♂), urobilinogen (2♂), bilirubin (1♂)

0.8% (0.24%) - Occult blood (2♂), urobilinogen (1♂)

**Autopsy:** No difference (Congestion of the lungs, hyperemia in renal lymph nodes were observed),**Mutagenicity Study:**

1. A mutagenicity study of compound B by use of microorganisms (Ames test). T. Mizuno, Central Research Laboratory, Maruishi Pharmaceutical Co., Ltd., Study CB-8M1A; (1988c). Compound B in the presence and absent of S-9 mix did not induce reverse mutation in Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 and Escherichia coli strain WP 2uvr. The results indicated that although some bacterial strains demonstrated a slight increase in revertant colony formation, the increment ratio was found to be less than two. A dose-dependency was also not observed. Positive controls showed strong mutagenicity.

**Summary of Toxicity Studies of Compound B**

Staggering gait, depressed locomotor movement and respiratory rate, dysbasia and prone position were observed in all Wistar rats treated with compound B by inhalation in the close system. No treatment related finding were observed at necropsy. The highest amount of compound B observed in the present study was 0.24% (2,400 ppm) which is ~1000 times as high as the amount formed during 2.7% sevoflurane circulation in the closed circulation system. Therefore, the safety of compound B is sound. Compound B was also established to be non-mutagenic using the Ames test.

### Overall Summary and Evaluation

Sevoflurane, a highly fluorinated derivative of methyl isopropyl ether, was synthesized at Travenol Laboratories during the late 1960s. It is a clear, colorless, nonpungent and nonflammable liquid with a specific gravity of 1.5 g/ml. This volatile anesthetic agent is approved for use in induction and maintenance of general anesthesia in Japan (1990), China (1992), Korea (1993), Peru (1994) and Argentina (1994). According to the sponsor "Sevoflurane has been safely administered to approximately 2 million Japanese patients".

**Pharmacology:** Sevoflurane has been demonstrated to be a fast acting, non-irritating anesthetic agent in a variety of animal species (mouse, rat, rabbit, dog, cat, swine and human). It is also associated with rapid recovery following discontinuation of anesthesia, due to its low blood-gas solubility. Mean MAC of sevoflurane for various species were 2.1 to 3.7%. The MAC for sevoflurane in human decreases with age (3.3 - 1.44%) and with the addition of nitrous oxide (2.02 - 0.72%).

The neuropharmacological effects of sevoflurane (0.8 - 9.5%) were studied in rabbits, dogs, cats, mice and rats. The anesthesia with sevoflurane was involved with the suppression of cerebral cortex activity (loss of awareness and motor reflexes), suppression of the cerebellum and mesencephalon (loss of righting reflex and corneal reflex), suppression of the spinal cord (loss of tail pinch response) and suppression of the medulla oblongata (depression of respiration). The relaxation of skeletal muscle in mice occurred faster with sevoflurane than with enflurane or halothane. It appears that sevoflurane in animals selectively inhibits the ascending reticular activating system and does not significantly affect the nucleus centrum medianum of the thalamus-cortical system. Sevoflurane administration in cats and rats produced a series of EEG changes including appearance of high-amplitude slow waves, burst suppression and onset of single spike in a dose-dependent manner (5 % & 9.5 %) similar to those observed with enflurane. Sevoflurane and isoflurane produced similar effects on cerebral blood flow, cerebral metabolic rate for oxygen and intracranial pressure (ICP) in rabbits. Unlike halothane and enflurane, sevoflurane did not increase ICP in dogs allowed to become hypotensive with increasing concentrations of anesthetic (0.5, 1.0 and 1.5 MAC).

Sevoflurane at equipotent concentration depressed blood flow and cardiac index in newborn swine to a lesser extent than did halothane or isoflurane. It did not reduce collaterally-derived myocardial perfusion or cause coronary steal. During a subacute inhalation study in monkeys (*Macaca speciosa*), minute volume and tidal volumes were not significantly altered by sevoflurane (1.5%) and halothane (1.5%). Arterial pressures indicated that both agents induced hypotension. Mean arterial pH and PCO<sub>2</sub> during sevoflurane anesthesia were within normal limits. Respiration and cardiovascular function remained adequate with sevoflurane and electrocardiographic abnormalities were not seen. All sevoflurane treated monkeys exhibited periods of electroencephalographic silence ("burst suppression"). Burst suppression was not observed with halothane, ether or methoxyflurane, but has been reported in monkeys anesthetized with BAX-3224, a fluorinated methyl-propyl ether similar to sevoflurane [*Anes Analg Cur Res* 1975; 54: 144 - 151]. No adverse effects associated with burst suppression were found in these animals.

Sevoflurane appears to have a lower risk for the potentiation of pressoramine-induced arrhythmias than either halothane or enflurane. The cardiovascular interaction between sevoflurane and the calcium channel blocker, nifedipine, appears to be additive similar to other inhalational anesthetic agents. In general the hemodynamic/cardiovascular effects of sevoflurane are comparable to those of isoflurane.

Similar to other inhalational anesthetics, sevoflurane produced respiratory depression with increasing depth of anesthesia. Sevoflurane produced a weak trigger of malignant hyperthermia in susceptible pigs than halothane. Unlike halothane, sevoflurane did not increase portal resistance in the isolated perfused rat liver.

**ADME:** The absorption of sevoflurane from the inspired air into the alveolar air is quite rapid and reasonably similar in dogs, swine and humans. Peak sevoflurane concentrations are related to the anesthetic dose and averaged 25-200  $\mu\text{g/ml}$ . The initial rapid elimination of sevoflurane from blood ( $0.58 \pm 0.03$  min) was faster than that of halothane ( $1.29 \pm 0.15$  min) in Sprague-Dawley rats (Anesth Analg 1990; 71:658-664). Similarly, the initial elimination of sevoflurane from the brain ( $1.60 \pm 0.10$  min) was faster than halothane ( $2.70 \pm 0.66$  min). The slower  $\beta$ -elimination rates from brain ( $\approx 34$  min), blood ( $\approx 30$  min) and adipose tissue ( $\approx 4$  hours) were similar for both volatile anesthetics. This data suggest that the postoperative psychomotor impairment caused by residual subanesthetic concentrations of anesthetic in tissue might be similar for both anesthetics in humans. Protein binding characteristics of sevoflurane are similar to those of other fluorinated inhalation anesthetics. CYP2E1 has been shown to be the main cytochrome P450 isoform responsible for the metabolism of sevoflurane in human, rats and rabbits. The elimination rates from the swine central (pulmonary) compartment were significantly different and decreased in the order of desflurane > sevoflurane > isoflurane > halothane. The rapid distribution into and elimination of sevoflurane from tissues is consistent with expectations based on its tissue/blood partition coefficients.

**Toxicology:** The calculated median lethal concentration for one hour sevoflurane inhalation exposures ranged from 5.8% in the rats to 10.6% in rabbits. Sevoflurane was less toxic in mice and rats when administered orally ( $\text{LD}_{50}$  16-37 mg/kg) or intraperitoneally ( $\text{LD}_{50}$  10-18 mg/kg). Toxic signs observed during acute studies were decreased locomotor movement, staggering gait, loss of righting reflex, suppression of respiration and piloerection. Prolonged exposure to rats (8 weeks), dogs (2 weeks) and monkeys (8 weeks) revealed an increase in serum enzyme activities (ALP, ALT, LDH, CPK, AST) in one or more species. Both sevoflurane and halothane treated dog groups showed focal pulmonary atelectasis and vacuolization of parenchymal cells of the liver. Body weights, hematology, urinalysis and histopathology revealed no apparent drug-related toxic effects in monkeys.

Sevoflurane did not effect the fertility and general reproductive performance of rats (Segment I). The no effect level of sevoflurane in rats during fetal organogenesis period (Segment II) appears to be 0.3 MAC. The reduction in fetal weights and increased skeletal variation observed at 1 MAC (2.2%) may be due to growth inhibition. In rabbits, teratogenic effects (Segment II) of sevoflurane without  $\text{CO}_2$  absorbent was not significant at 1.0 MAC (1.8%). The no effect levels of sevoflurane during perinatal and postnatal study (Segment III) in rats may be 0.3 MAC for dams (P) and offsprings (F1) and 1 MAC for fetuses (F2) at the last stage of gestation.

Since sevoflurane did not show any mutagenic effect in the reversion test with bacteria, mouse micronucleus assay, lymphoma mutagenicity assay, cell transformation assay in Balb/c-3T3 cells, chromosomal aberration test with Chinese hamster lung cells in culture, and  $^{32}\text{P}$  post-labeling DNA adduct formation in mouse liver, it may be concluded that sevoflurane is not mutagenic.

**Metabolites:** Sevoflurane is metabolized to hexafluoroisopropanol (HFIP) and inorganic fluoride is released. The acute  $\text{LC}_{50}$  of HFIP in Sic Wistar rats following a single 3-hour inhalation exposure was approximately 0.185% indicating that HFIP is more toxic than sevoflurane. The acute  $\text{LD}_{50}$

following intraperitoneal or intravenous injection in rats were 0.14 - 0.2 mg/kg and 0.10 - 0.11 mg/kg, respectively. Intraperitoneal HFIP injections were associated with tissue adhesion and hepatic deformation. HFIP was not mutagenic in a reverse mutation (Ames) assay.

HFIP is conjugated with glucuronic acid. Cytochrome P450 2E1 is the main isoform identified for sevoflurane metabolism. Classical inducers such as phenobarbital and phenytoin do not induce this isoform of P450 in human. Therefore, barbiturates and phenytoin would be expected to have little or no effect on Sevoflurane defluorination. Other P450 2E1 inducer such as isoniazid, chronic ethanol consumption, untreated diabetes and prolong fasting would be expected to stimulate sevoflurane defluorination.

Metabolism of sevoflurane results in the generation of inorganic fluoride, which is known to be nephrotoxic (JAMA 1973; 225; 1611-1616). Acute toxicity studies in albino rats (1 MAC) and dogs (1.7 MAC) did not reveal nephrotoxicity (urinary osmolality, Na, K, electrolytes and volume, serum creatine and BUN values and renal histopathology) indicating that fluoride concentrations did not reach levels presumably associated with nephrotoxicity ( $\geq 50 \mu\text{M}$ ). This fluoride-induced nephrotoxicity has not been encountered during the development and marketing of sevoflurane in Japan despite maximum inorganic concentration  $\geq 50 \mu\text{M}$  in some patients. In humans, the rapid pulmonary elimination of sevoflurane minimizes the amount of anesthetic available for metabolism (<5% metabolism). After sevoflurane exposure, the inorganic fluoride concentrations usually peak within 2 hours of anesthesia and return to baseline levels within 48 hours post-anesthesia. The minimal intrarenal defluorination may explain the lack of nephrotoxicity of sevoflurane.

**Degradant/Impurity:** Sevoflurane in direct contact with  $\text{CO}_2$  absorbants (Soda Lime and Baralyme) produces Compound A (pentafluoroisopropenyl fluoromethyl ether, [PIFE],  $\text{C}_4\text{H}_2\text{F}_6\text{O}$ ) and Compound B (pentafluoromethoxy isopropyl fluoromethyl ether, [PMFE],  $\text{C}_5\text{H}_6\text{F}_6\text{O}$ ). Compound A exposure to rats was associated with renal tubular necrosis, mineralization, and tubular epithelial hyperplasia. The threshold for renal injury was 25 - 50 ppm exposure; however as the exposure time is increased the threshold will drop. At 32 ppm, a concentration that has been reported to occur in the clinic, renal toxicity to the rat may be expected to occur, especially if the exposure time is prolonged. Other toxic effects reported for compound A were degeneration and desquamation of the nasal turbinates at 202 ppm and pulmonary congestion and edema at exposure of  $\geq 175$  ppm for six hours. Small pyknotic neuronal nuclei with eosinophilic cytoplasm were reported in the brain of rats exposed to  $\geq 350$  ppm for three hours. Hepatic injury, such as periportal fatty infiltration, hepatic swelling, and occasional pyknotic hepatocyte nuclei were observed in rats exposed to  $\geq 300$  ppm. Compound A was negative in the Ames test, in the chromosome aberration test with a newborn Chinese hamster lung fibroblast cell line, and did not produce anaphylactic reactions in the guinea pig.

The renal toxicity of Compound A appears to be comparable to that for BCDFE (2-bromo-2-chloro,1,1-difluoro ethylene) at concentration of 60 ppm. BCDFE is a metabolite as well as a degradant of halothane. It is a known nephrotoxic in mice. Strum et al (Anesth Analg 1994; 78: 340-348) have recently demonstrated that the degradation, absorption, and solubility of volatile anesthetics in soda lime depend on water content. Baralyme produced higher concentrations of degradation products than soda lime in low flow (1 l/min) anesthesia with sevoflurane (Anesthesiology 1994; 81: 340-345). During clinical trials, the mean maximum concentration of Compound A measured in the presence of soda lime in the anesthesia circuit at a flow rate of 0.5 L/min was  $19 \pm 6.38$  ppm (range 12-32 ppm). In children, the maximum concentration of Compound A was  $7.3 \pm 3.9$  ppm (maximum concentration = 15 ppm, 0.0015%) at a flow rate of 2 L/min. According to the sponsor "Data from approximately 2 million patients indicate that Sevoflurane does not adversely affect renal function".

This lack of nephrotoxicity of Compound A in humans may be due to a lower rate of conjugate formation (activity of  $\beta$ -lyase, an enzyme abundantly found in the renal cortex) and/or a more rapid biotransformation of Compound A (oxidative pathway, P450 2E1 activity) in humans than in rats.

Compound B did not effect renal parameters or tissue pathology in rats at concentrations up to 2,400 ppm (0.24%) for three hours and was not mutagenic in a reverse mutation (Ames) test.

As predicted by the results of the animal studies, the incidence of adverse experiences related to sevoflurane has been small and comparable to that found with other anesthetic agents. Therefore, it is concluded that sevoflurane is a reasonably safe and effective volatile anesthetic under most anesthetic conditions.

#### Recommendations

This NDA is approvable from the pharmacology/toxicology point of view. The following underlined additions in the pregnancy category should be added.

#### Pregnancy Category B:

Reproduction studies have been performed in rats and rabbits at doses up to 1 MAC (minimum alveolar concentration) without  $\text{CO}_2$  absorbant and have revealed no evidence of impaired fertility or harm to the fetus due to sevoflurane at 0.3 MAC, the highest nontoxic dose. Developmental and reproductive toxicity studies of sevoflurane in animals in the presence of strong alkalies (i.e., degradation of sevoflurane and production of compound A) have not been conducted. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, sevoflurane should be used during pregnancy only if clearly needed.

*Anwar Goheer*  
Anwar Goheer  
12/6/94

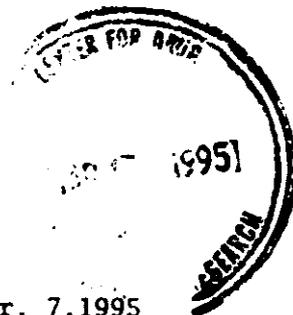
*Will Coulter*  
Will Coulter

Concur by peer reviewer:

*Lucy Jean*  
Lucy Jean

cc:  
IND  
HFD-007/Division File  
/MAGoheer  
/AWCoulter  
/LVaccari  
HFD-345

MAR 29 1995



DMF Title: SEVOFLURANE

1. CHEMIST REVIEW: #2 2. REVIEW DATE: Mar. 7, 1995

3. DMF INFORMATION REVIEWED:

<u>Type of Submission</u>	<u>Date of Submission</u>	<u>Location of Information</u>
Amendment	22-12-94	1.1

4. PREVIOUS DOCUMENTS

<u>Type of Document</u>	<u>Date of Document</u>	<u>Comment</u>
NONE		

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

NAME:  
ADDRESS:

REPRESENTATIVE:  
TELEPHONE:

U.S. AGENT  
NAME:  
ADDRESS:

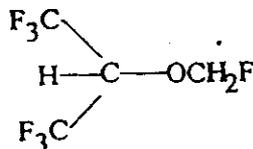
REPRESENTATIVE :  
TELEPHONE:

6. ITEM REVIEWED:

NAME: Sevoflurane  
CHEMICAL NAME: Fluoromethyl 2,2,2,-trifluoro-1-(trifluoromethyl) ethyl ether

CAS:  
MOLECULAR WEIGHT: 200.5  
CHEMICAL FORMULA: C H F O  
4 3 7

STRUCTURAL FORMULA:



7. DMF REFERENCED FOR:

NDA 20-478  
 APPLICANT NAME: Abbott Laboratories  
 LOA DATE: Jul. 29, 1994  
 DRUG PRODUCT NAME: Sevoflurane  
 DOSAGE FORM: Volatile Liquid  
 STRENGTH: 250 ml  
 ROUTE OF ADMINISTRATION: Inhalation

8. SUPPORTING DOCUMENTS: DMF TYPE9. CURRENT STATUS OF DMF:

DATE OF LAST UPDATE: Dec. 27, 1994  
 DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA'S  
 HAVE BEEN PROVIDED: None

10. CONSULTS: None11. REMARKS/COMMENTS:

Refer to review notes for substance of  
 review

12. CONCLUSION/RECOMMENDATIONS:

The firm has responded to the questions sent Dec. 21, 1994.

We find the responses satisfactory.

  
 Review Chemist  
 HFD-007

CC:  
 DMF  
 HFD/007/Div. File NDA 20-478  
 HFD-007/JMRoss  
 HFD-007/Vaccari  
 R/D Init by: PMaturu *P Maturu*  
 F/T by JMRoss/3-7-95 *3-29-95*  
 WPPFILES\DMF

VAC LARI

PILOT DRUG EVALUATION STAFF HFD-007  
Review of Chemistry, Manufacturing, and Controls

NDA: 20-478

MAR 7 1995

CHEMISTRY REVIEW: 2

DATE REVIEWED:

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	02-05-94	02-05-94	
Amendment	05-01-95	09-01-95	
Amendment	12-01-95	17-01-95	
Amendment	23-01-95	25-01-95	
Amendment	22-12-94	27-12-94	(DMF 11132)
Amendment	25- 2-95	1- 3-95	

NAME & ADDRESS OF APPLICANT:

Abbott Laboratories  
One Abbott Park Road  
Abbott Park, IL. 60064

DRUG PRODUCT NAME

Proprietary:

Nonproprietary/Established/USAN: Sevoflurane

Code Name/#: 74341

Chem. Type/Ther. Class:

PHARMACOLOGICAL CATEGORY/INDICATION:

Anesthetic agent/Inhalational/ induction and maintenance of anesthesia

DOSAGE FORM:

Volatile Liquid

STRENGTHS:

250 ML

ROUTE OF ADMINISTRATION:

Inhalation

DISPENSED:

Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name:

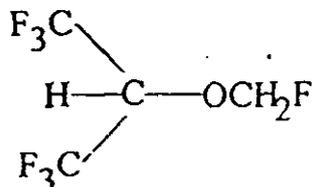
Fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl) ethyl ether.

British Approved Name:

1,1,1,3,3,3-hexafluoro-2-fluoro methoxypropane

Other Name:

Sevofrane ® in Japan



Molecular Formula:

C<sub>4</sub>H<sub>3</sub>F<sub>7</sub>O

Molecular Weight:

200.05

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS:

Mazze, M.D.: The Safety of Sevoflurane in Humans,  
Anesthesiology 77: 1062-1063, 1992

CONSULTS:

No consults outside the Division

REMARKS:

Inspections have been requested as of 12/1/94

Analytical methods have been sent out for validation

The Labeling and Nomenclature Committee approved the  
trade name, Ultane.

Labeling has been found satisfactory, with some revisions  
that have been discussed with the firm.

The Anesthetic and Life Support Drug Advisory Committee met on Jan, 17-18,1995.

Sevoflurane was found approvable and certain safety issues could be dealt with in a postmarketing fashion. Specifically, these are:

- toxicity of Compound A
- use of this drug in renally impaired patients
- use of sevoflurane inpatients taking drugs which could enhance its metabolism

CONCLUSION/RECOMMENDATIONS:

The following pages contain amendments with the firms responses to FDA's questions. In addition the Comments are my final concerns to their responses. The last page contains a question I have faxed to the firm.

It appears if the inspections are satisfactory this application will be approved

Orig. NDA 20-478  
HFD-007/Div. File  
HFD-007/JMROSS/2-23-95  
HFD-007/Vaccari  
F/T By: JMROSS/2-23-95  
R/D Init. By: PMaturu

~~NOT REC~~ f Melara  
SATISFACTORY. Sec. Rev. Chem.  
PT1/3-7-95

*Juanita Ross*

Review Chemist

AMENDMENT

January 23, 1995

NDA 20-478

Page 4.

Request: "1. Under Purity Profile in your presubmission follows:

is defined as

COMMENT:

✓

Response is acceptable.

Request: "2. In the same paragraph on page 45, the following statement is made ..

"Other impurities which arise from the route of synthesis and purification such as  
are normally not found in the product"

Yet how do you explain the following hydrolysis reaction : ....."

/

Response:

COMMENT:

Response is acceptable.

Request: "3. The firm indicates that the single largest impurity other than Compound A is Compound M. Are we to assume that the reference to Other Single Largest Impurity Test stated in the Test and Final Product Specifications and in the Stability Report is referring to Compound M? Explain."

Response:

COMMENT: Response is acceptable.

Request: "4. Based on the dates of bulk manufacturing that was submitted for various lots in your response dated Jan. 5, 1995 and your indication of a 24 months proposed expiration date, there should certainly be enough data to submit up to two years in at least three lots.

With this in mind, I would like to have a complete set of data for at least three lots in the format similar to the one shown on pages 254-257 of your presubmission CMC section. I would like to have a transparency included for the meeting on Jan. 17, 1995, since with all the opinions concerning the quality of this finished product, it would be wise to have this information on hand if the committee requests it."

Response: Appended in Attachment 2 is updated stability data through 12 months. The filling date of the finished product at Rocky Mount was 7/31/93. Therefore, 24 month data will not be available until 8/95.

COMMENT: In the two attached pages, I have created a table, showing the data reported for the initial time and at twelve months under 30°C. for six lots. So far the data appears to be within acceptable specification limits.



2 PAGES  
PURGED

111R =  
INV = Inverted  
U60 = Upright, 60 % Relative  
.. = All results are for Alkalinity

- ① Bacteria, fungi and *E. coli* were not detected in bulk sevoflurane.
- ② Bacteria decreased rapidly in sevoflurane and almost died after 24 or 48 hrs.
- ③ *B. subtilis* was considered it had a bit of resistivity against sevoflurane, but it was confirmed that when incubation cell is for by one digit, it died very rapidly in sevoflurane.
- ④ *B. subtilis* spore showed resistivity differently from vegetative cells, but it was found that it decreased as the time passed.
- ⑤ Fungi, mold and yeast showed the decreasing tendency, but they did not die even if 5 days later.

From above conclusion, even if sevoflurane is contaminated with indicator cell used here (or microorganisms which have similar characteristic), it is considered that the possibility of growth of microorganisms in sevoflurane is low.

#### 4.2.3 Physical and Chemical Characteristics

	<u>Sevoflurane</u>
Boiling Point at 760 mm Hg:	58.6 °C
Specific Gravity at 20 °C:	1.520 - 1.525
Vapor Density (air = 1.0g/L):	6.9 g/L*
Vapor Pressure in mm Hg:	157 mm Hg at 20 °C 197 mm Hg at 25 °C 317 mm Hg at 36 °C

\* The vapor density was calculated based on the molecular weights of *Sevoflurane* (200.05) and air (28.8).

#### Distribution Partition Coefficients at 37 °C:

Blood/Gas  
Water/Gas  
Lard Fat/Gas  
Olive Oil/Gas

#### Main Component/Gas Partition Coefficients at :

Conductive rubber  
Beryl rubber  
Polyvinyl chloride (endotracheal tube)  
Polyethylene (circuit tube)

N/A = not applicable

VACCARI

DEC 9 1994

PILOT DRUG EVALUATION STAFF HFD-007  
Review of Chemistry, Manufacturing, and Controls

NDA: 20-478

CHEMISTRY REVIEW: 1

DATE REVIEWED:

SUBMISSION TYPE

DOCUMENT DATE

CDER DATE

ASSIGNED DATE

Original

29~~6~~ April 94  
02-05-94

02-05-94

06-05-94

NAME & ADDRESS OF APPLICANT:

Abbott Laboratories  
One Abbott Park Road  
Abbott Park, IL. 60064

DRUG PRODUCT NAME

Proprietary:

Nonproprietary/Established/USAN: Sevoflurane

Code Name/#: 74341

Chem. Type/Ther. Class:

PHARMACOLOGICAL CATEGORY/INDICATION:

Anesthetic  
agent/Inhalational/  
induction and maintenance  
of anesthesia

DOSAGE FORM:

Volatile Liquid

STRENGTHS:

250 ML

ROUTE OF ADMINISTRATION:

Inhalation

DISPENSED:

Rx                      OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name:

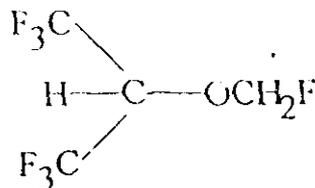
Fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl) ethyl ether.

British Approved Name:

1,1,1,3,3,3-hexafluoro-2-fluoro methoxypropane

Other Name:

Sevofrane ® in Japan



Molecular Formula

C<sub>4</sub>H<sub>3</sub>F<sub>7</sub>O

Molecular Weight

200.05

SUPPORTING DOCUMENTS:RELATED DOCUMENTS:

Mazze, M.D.: The Safety of Sevoflurane in Humans,  
Anesthesiology 77: 1062-1063, 1992

CONSULTS:

No consults outside the Division

REMARKS:

Inspections have been requested as of 12/1/94.

Analytical Methods have yet to be validated.

Refer to "Review Notes" for substance of the review.

The firm's proposed trade name of SEVORANE was turned down by our CDER Labeling and Nomenclature Committee, because of its similarity to the established name.

CONCLUSION/RECOMMENDATIONS:

Several deficiencies were noted and from a chemist viewpoint should be resolved before approval.  
SEE "Draft Deficiency Letters"

- a.) Applicant
- b.) Drug Master File Holder,

**\*\*\*SENSITIVE\*\*\***

**REVIEW**

**OF**

**ENVIRONMENTAL ASSESSMENT**

**FOR**

**NDA 20-478**

**Sevorane**

**(sevoflurane)**

**HFD-007 REVIEW DIVISION**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**HFD-102**

**DATE COMPLETED 1/04/95**

## EA Review for NDA 20-478

Second review for review of amended EA information dated November 16, 1994 and December 16, 1994 for NDA 20-478 Sevoflurane (sevoflurane). Primary review with deficiencies conducted by A. Mukhejee.

This secondary review has primarily reviewed the material submitted in response to the deficiency letter.

### Item 4

The deficiency letter requested information on the environmental surroundings for all sites of manufacture, and disposal. Estimate amount of drug substance used.

#### Response by applicant:

Adequate. Information was submitted in the 11/16/94 amendment on each manufacturing, distribution and disposal site. This amendment also contains the information on estimated amount of use of drug substance. There amount of unused drug was also provided. Based on this information, there appears to be no significant environmental concern from the use or the disposal of the unused drug substance.

### Item 5

Provide the structure and physicochemical properties of impurities. Provide a clear copy of the MSDS.

#### Response by applicant:

Adequate. Impurity information was submitted in the 11/16/94 amendment. A new MSDS was submitted that is legible. The impurities do not appear to be a significant environmental concern.

### Item 6

Please provide emissions information and compliance information from the Japanese facility. Provide a product specific compliance letter for production of the drug at the Rocky Mtn. facility. Provide estimated amount of return and off-spec drugs. Provide MEEC.

#### Response by applicant:

Adequate. This information was provided in the 11/16/94 amendment. Based on the MEEC and effects data, the concentrations in the environment of the drug product from use there does not appear to be a concern. Compliance information is also included for emissions from production and disposal.

#### Additional information requests:

After review of the original EA submission, the EA review, and the response to the deficiency letter, we determined there remained a potential concern about the air emissions of the drug substance from the Rocky Mountain plant. According to page 7 (or 8) of the EA, it is estimated that approximately \_\_\_\_\_ of drug substance is expected to be emitted into the atmosphere ecosystem (based on 5th year production expectations). This is approx. \_\_\_\_\_ of the expected production volume. According to the air permits submitted for this site, the facility is in compliance with their permit limits. I verified with the applicant that the \_\_\_\_\_ kg/yr was the actual expected emissions. I was assured that it was. Consequently I consulted with Phil Vincent and we asked the applicant to submit information of degradation and stability of the drug substance. This information was submitted in the 12/16/94 response.

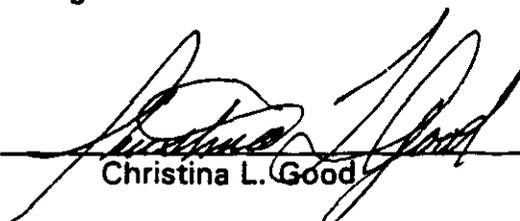
Based on this information, and the information contained in the original and 11/16/94 submissions, we have concluded that these air emissions will not affect the environment significantly. The dispersion of the drug substance in the atmosphere will most likely be enough to limit the concentration below any NOEC value reported.

We also requested a non-confidential version of the EA for the public docket. This was submitted as part of the 12/16/94 amendment.

The production, use and disposal of the drug product does not appear significantly affect the human environment. This conclusion is based on the information contained in the EA, the amendments to the EA's, and the EA review.

File:20478ea2.rcg

Prepared by

  
Christina L. Good 1/4/95

concur: Phil Vincent

  
01/04/95

cc:

HFD-007/LVaccari

HFD-102/Good

HFD-102/Vincent

HFD-102/file no20478

**FINDING OF NO SIGNIFICANT IMPACT**

**AND**

**ENVIRONMENTAL ASSESSMENT**

**FOR**

**NDA 20-478**

**Sevorane (sevoflurane)**

**CENTER FOR DRUG EVALUATION  
AND RESEARCH**

**HFD-007**

**FINDING OF NO SIGNIFICANT IMPACT**  
**NDA 20-478**

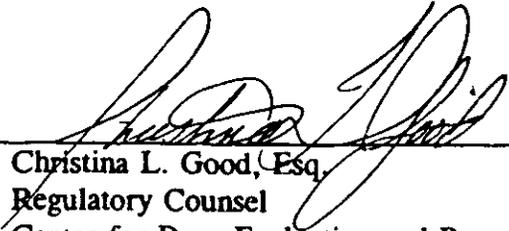
The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy. Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

FDA's Center for Drug Evaluation and Research (CDER) has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

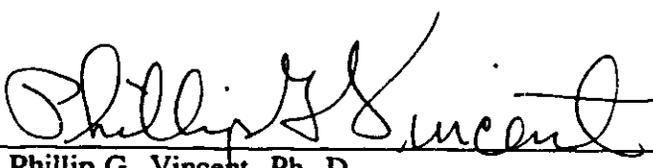
In support of their new drug application for Sevorane (sevoflurane), Abbott Laboratories prepared an abbreviated environmental assessment (EA) (21 CFR 25.31a(b)(3)) (attached) based on the fact that this is a general anesthesia drug. The abbreviated EA evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

CDER has concluded that the product can be manufactured and used without any expected adverse environmental effects. The concentrations to be emitted at the site of manufacture of the bulk product are in conformance with the environmental laws of Japan. The concentrations to be emitted at the packaging site are not expected to be at levels to cause any environmental effects. Precautions at the manufacture facilities also are expected to minimize occupational exposures and environmental release. Any residues of Sevorane or its degradation product entering the environment as a result of administering the drug to humans are expected to be in such low concentrations as to not be toxic to organisms. Accidental spill control procedures are available. Disposal will be in accordance with appropriate waste procedures.

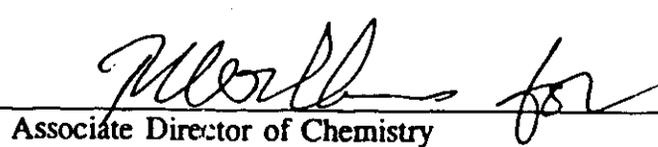
1/4/95  
DATE

  
Christina L. Good, Esq.  
Regulatory Counsel  
Center for Drug Evaluation and Research

1/5/95  
DATE

  
Phillip G. Vincent, Ph. D.  
Environmental Assessment Officer  
Center for Drug Evaluation and Research

1/4/95  
DATE

  
Associate Director of Chemistry  
Center for Drug Evaluation and Research

Attachment:

FOI Copy of Environmental Assessment for Sevorane NDA 20-478



Hospital Products Division

Abbott Laboratories  
D-380, Bldg. AP30  
200 Abbott Park Road  
Abbott Park, Illinois 60064-3537

March 21, 1995

CENTER FOR DRUG EVALUATION AND RESEARCH  
PILOT DRUG EVALUATION STAFF, HFD #007  
Attn: DOCUMENT CONTROL ROOM #9B-23  
5600 Fishers Lane  
Rockville, Maryland 20857-1706

ATTENTION: Robert Bedford, M.D.  
Acting Director

Re: NDA 20-478 Ultane™ (sevoflurane)

Abbott Laboratories hereby amends the above-referenced New Drug Application to provide a debarment statement. Appended is the required statement.

We trust that this information is complete.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson  
Director,  
Regulatory Affairs  
Hospital Products Division  
(708) 937-3213

DTG/dg  
Attachment  
3-95fda.dtg





**CERTIFICATION REQUIREMENT FOR ALL APPLICATIONS**

**FOR APPROVAL OF A DRUG PRODUCT**

**CONCERNING USING SERVICES OF DEBARRED PERSONS**

Under the new law, any application for approval of a drug product submitted on or after June 1, 1992, must include:

"a certification that the applicant did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)], in connection with such application."

*Abbott Laboratories certifies that it did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)], in connection with this application.*

Frederick A. Gustafson  
Director, Regulatory Affairs  
Hospital Products Division  
AP30  
Abbott Laboratories  
200 Abbott Road  
Abbott Park, Illinois 60064-3537

3/20/95  
Date



**Hospital Products Division**

---

Abbott Laboratories  
D-399, Bldg. AP30  
200 Abbott Park Road  
Abbott Park, Illinois 60064-3537

March 17, 1995

CENTER FOR DRUG EVALUATION AND RESEARCH  
PILOT DRUG EVALUATION STAFF, HFD #007  
Attn: DOCUMENT CONTROL ROOM #9B-23  
5600 Fishers Lane  
Rockville, Maryland 20857-1706

ATTENTION: Robert Bedford, M.D.  
Acting Director

Re: NDA 20-478 Ultane™ (sevoflurane)

Abbott Laboratories hereby amends the above-referenced New Drug Application, as requested in the January 6, 1995 letter to industry from Robert T. O'Neill, Ph.D., Acting Director, Office of Epidemiology and Biostatistics, to provide a statement on the use of flawed Pentium chips. As stated in the referenced communication, the Agency has requested that all sponsors with pending NDA or NDA supplements inform the appropriate medical review division within CDER, as to whether the submission contained analyses carried out using a flawed Pentium chip.

We have verified that the computer equipment used in the analysis of data included in the subject NDA did not utilize a flawed Pentium chip.

We trust that this information is complete.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson  
Director,  
Regulatory Affairs  
Hospital Products Division  
(708) 937-3213

DTG/dg  
3-95fda.dtg

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: Sept 22, 1994

From: Asoke Mukherjee Ph.D., HFD-102

Through: Phillip G. Vincent Ph.D., HFD-102

Subject: EA for Servoflurane, NDA 20-478

To: Leslie Vacarri, HFD-007

The initial review of the abbreviated EA submitted on April 29, 1994 has been completed. Following recommendation and comments have been suggested by the reviewer.

1. For item # 4:

Provide the environment surrounding each of the production, distribution and disposal sites. Estimated amount of use in kg/lbs/liter per year need to be mentioned. Also amount of the drug substance that would be disposed as unused drug product per year on the fifth year of production needs to be specified. Provide the address and environment surrounding the site where recovery and disposal of the returned goods would be made in this item.

2. For item # 5:

Provide structure and physicochemical properties of impurities (if any) in this section. Provide a better copy of the material safety data sheet for the drug substance.

3. For item #6:

Provide estimated emission of the drug substance and other materials related to the synthesis of servoflurane from the facilities per year on the fifth year of production. State what type of control would be taken to minimize emission. Provide state, local and federal environmental compliance letter issued to the specific to the product. Certified copy of the English version should be included. Also provide product specific compliance letter from the appropriate local, state and federal authorities for the air and water emission of servoflurane from the Rocky Mountain plant, and for the site of disposal of returned and off specification product. Provide estimated amount of returned and off specification product per year for the fifth year of production in this section also. MEEC data need to be mentioned in this item of the EA.

NDA 20478

ULTANE

4 OF 4

Page 2  
NDA20-478

Endorsement:

HFD-102/007 Asoke Mukherjee Ph.D.  
Pharmacologist

HFD-102/P.G. Vincent Ph.D.

c.c: Original NDA 20-478  
EA file  
Div File HFD-007  
Supervisory Chemist/ HFD-007

*Asoke Mukherjee*

*B.G. Vincent*

OCT 4 1994

Consult #395 (HFD-007)

ULTANE

Sevoflurane

A review revealed one name which looks like the proposed name: Altace. However, due to differences in dosage forms, the Committee does not believe there is a significant possibility of confusion involving the two names.

The Committee has no reason to find the proposed name unacceptable.

CDER Labeling and Nomenclature Committee

*Yana Ruth Miller*, Chair 2/4/95.

#395

MEMORANDUM

TO: CDER Labeling and Nomenclature Committee  
Attention: Yana Mille, Chair, (HFD-638) MPN2 204

FROM: Pilot Drug Evaluation Staff, HFD-007  
Attention: Robert Bedford, M.D., Reviewing Medical Officer  
Leslie Vaccari, CSO

*Leslie Vaccari 12-27-94*

DATE: December 27, 1994

SUBJECT: Request for Assessment of Proprietary Name of a Proposed Drug Product

Proposed Proprietary Name: Ultane

Established name, including dosage form: sevofluane liquid anesthetic for  
general anesthesia, 250 mL

Other proprietary names by the same firm for companion products: none

Indications for Use: general anesthesia

Comments: Refer to consult #338 sent 8-22-94 for Sevoflurane (sevoflurane).  
Sponsor was notified of your finding dated 10-11-94 that Sevoflurane was  
unacceptable. This is their new proposed name.

Labeling Committee Recommendations:



Hospital Products Division

Abbott Laboratories  
D-389, Bldg. AP30  
200 Abbott Park Road  
Abbott Park, Illinois 60064-3537

March 8, 1995

CENTER FOR DRUG EVALUATION AND RESEARCH  
PILOT DRUG EVALUATION STAFF, HFD #007  
Attn: DOCUMENT CONTROL ROOM #9E-23  
5600 Fishers Lane  
Rockville, Maryland 20857-1706

ATTENTION: Robert Bedford, M.D.  
Acting Director

Re: NDA 20-478 Sevorane® (sevoflurane)

Abbott Laboratories hereby amends the November 21, 1994 Safety Update to the subject New Drug Application (NDA). This amendment provides an additional safety report that has been recently received by Abbott Laboratories since the time of the update.

We trust that this information is complete.

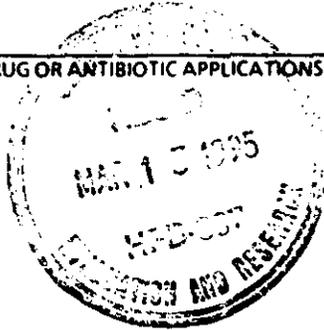
Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson  
Director, Regulatory Affairs  
Hospital Products Division  
Phone: (708) 937-3213  
Fax: (708) 938-7867

DTG/dg  
attachment  
G:\dtg\11-94fda.dtg



<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES</b> <b>PUBLIC HEALTH SERVICE</b> <b>FOOD AND DRUG ADMINISTRATION</b>		Form Approved: OMB No. 0910-0001 Expiration Date: March 31, 1990. See OMB Statement on Page 3.	
<b>APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE</b> <b>OR AN ANTIBIOTIC DRUG FOR HUMAN USE</b> <i>(Title 21, Code of Federal Regulations, 314)</i>		<b>FOR FDA USE ONLY</b>	
		DATE RECEIVED	DATE FILED
		DIVISION ASSIGNED	NDA/ANDA NO. ASS
NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).			
NAME OF APPLICANT Abbott Laboratories		DATE OF SUBMISSION March 8, 1995	
ADDRESS (Number, Street, City, State and Zip Code) Hospital Products Division - Div 23681 (D-389) 200 Abbott Park Road Abbott Park, Il 60064		TELEPHONE NO (Include Area Code) (708) 937-3213	
		NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued) 20-478	
<b>DRUG PRODUCT</b>			
ESTABLISHED NAME (e.g., USPI/USAN) N/A		PROPRIETARY NAME (If any) Sevorane TM	
CODE NAME (If any) Sevoflurane		CHEMICAL NAME fluoromethyl-2,2,2-trifluoro-1-(trifluoro- methyl) ethyl ether	
DOSAGE FORM Liquid		ROUTE OF ADMINISTRATION Inhalation	STRENGTH(S) N/A
PROPOSED INDICATIONS FOR USE Induction and maintenance of anesthesia.			
LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21CFR 314.420) REFERRED TO IN THIS APPLICATION:			
			
<b>INFORMATION ON APPLICATION</b>			
TYPE OF APPLICATION (Check one)			
<input type="checkbox"/> THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) <input type="checkbox"/> THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)			
IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION			
NAME OF DRUG		HOLDER OF APPROVED APPLICATION	
STATUS OF APPLICATION (Check one)			
<input checked="" type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ORIGINAL APPLICATION		<input checked="" type="checkbox"/> AN AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION	
<input type="checkbox"/> SUPPLEMENTAL APPLICATION			
PROPOSED MARKETING STATUS (Check one)			
<input checked="" type="checkbox"/> APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx)		<input type="checkbox"/> APPLICATION FOR AN OVER - THE - COUNTER PRODUCT (OTC)	

**CONTENTS OF APPLICATION**

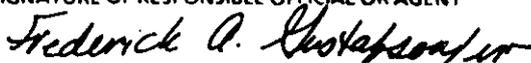
This application contains the following items: *(Check all that apply)*

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
<input type="checkbox"/>	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
<input type="checkbox"/>	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
<input checked="" type="checkbox"/>	c. Labeling (21 CFR 314.50 (e) (2) (ii))
<input type="checkbox"/>	i. draft labeling (4 copies)
<input type="checkbox"/>	ii. final printed labeling (12 copies)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
<input type="checkbox"/>	7. Microbiology section (21 CFR 314.50 (d) (4))
<input type="checkbox"/>	8. Clinical data section (21 CFR 314.50 (d) (5))
<input type="checkbox"/>	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
<input type="checkbox"/>	10. Statistical section (21 CFR 314.50 (d) (6))
<input type="checkbox"/>	11. Case report tabulations (21 CFR 314.50 (f) (1))
<input type="checkbox"/>	12. Case reports forms (21 CFR 314.50 (f) (1))
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
<input type="checkbox"/>	15. OTHER (Specify)

**Safety report**  
 I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT Frederick A. Gustafson	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	DATE 3/08/95
ADDRESS (Street, City, State, Zip Code) One Abbott Park Rd Abbott Park, Illinois 60064		TELEPHONE NO. (Include Area Code) (708) 937-3213

**(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec.1001.)**



Food and Drug Administration  
Rockville MD 20857

MAR - 2 1995

**TRANSMITTED VIA FACSIMILE**

David T. Guzek  
Director, Regulatory Administration  
Hospital Products Division  
Abbott Laboratories  
D-389, Bldg. AP30  
One Abbott Park  
Abbott Park, Illinois 60064-3500

RE: NDA# 20-478  
Ultane (sevoflurane)  
MACMIS ID #3032

Dear Mr. Guzek:

The Division of Drug Marketing, Advertising and Communications (DDMAC) has received Abbott Laboratories' (Abbott) February 21, 1995, request for an advisory opinion for the proposed logo which now incorporates sevoflurane's new proposed name, Ultane. DDMAC notes that should the name be rejected and another product name be required, the presentation of the logo would be retained.

At this time, DDMAC cannot comment on the proposed name, Ultane, as submitted until Abbott has received approval for the product name. DDMAC recommends that Abbott not engage in the use of promotions that use the proposed product name or logo before it is cleared by the new drug reviewing division. However, DDMAC has no objections to the proposed logo as presented.

If Abbott has any questions or comments, please contact the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-240, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds Abbott that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #3032 in addition to the NDA number.

Sincerely yours,

*Jean E. Raymond, P.A.*

Jean E. Raymond, P.A.  
Regulatory Review Officer  
Division of Drug Marketing,  
Advertising and Communications



FDA 20-478

Food and Drug Administration  
Rockville MD 20857

Abbott  
Hospital Products Division  
Abbott Laboratories  
One Abbott Park Road  
Abbott Park, Illinois 60064-3500

DEC 23 1994

Attention: Frederick A. Gustafson  
Director, Regulatory Affairs  
Hospital Products Division

Dear Mr. Gustafson:

Please refer to your pending July 11, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Sevoflurane (sevoflurane) liquid anesthetic for general anesthesia 250 mL.

We have completed our review of the Chemistry section of your submission and have identified the following deficiencies:

1. On pages 239-244, data was submitted for 36 lots of bulk drug manufactured in Japan tested as per current test batch methods.

Batches:

# C-1,2,3,5,6,7,8,9,10,12,13,14,15,16,  
17,18,19,20,21,23,24,25,26,27,28  
#71104, #00210, #11224, #1120061

- a.) Clarify the absence of such information as:
  - Date these batches were manufactured
  - Date these batches were tested
  - Explain the batch numbering system.
- b.) For all the above batches clarify the absence of the following data:
  - Refractive Index
  - Identification (IR)/include copies of spectra
  - Fluoride Ions
  - Largest Single impurity
  - Acidity/Alkalinity - the word "Pass" is not acceptable, include actual data.
- c.) Include the chemical names of Compound A, Largest Single Impurity and any of the known Total Impurities in your Tables.
- d.) On pages 239 to 243, some of the values for Largest Total Impurities as out of specification limits. Please explain.



Table XXXXI Stability Data (continued) 250 mL Screw Cap Closure System (Reclaim Product)										
Test Performed:			Fluoride	Acidity** or Alkalinity	Non- volatile Residues	Water Content	Total Imp. w/o Cpd. A	Cpd. A	Other Largest Imp.	Severe Partic.
Test Method Assignment:										
Final Specifications:			NMT	NMT	NMT	NMT	NMT	NMT	NMT	NLT
Lot # / Stability #	Temp	Month/ Position	Results							

5. Clarify the revised specification in your stability protocol for Compound A in Appendix J, Page 492 of

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Leslie Vaccari  
Consumer Safety Officer  
(301) 443-3741

Sincerely yours,

Juanita Ross  
Chemist  
Pilot Drug Evaluation Staff, HFD-007  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research



Hospital Products Division

Abbott Laboratories  
D-389, Bldg. AP30  
200 Abbott Park Road  
Abbott Park, Illinois 60064-3537

December 22, 1994

ORIG AMENDMENT-

N(BZ)

CENTER FOR DRUG EVALUATION AND RESEARCH  
PILOT DRUG EVALUATION STAFF, HFD #007  
Attn: DOCUMENT CONTROL ROOM #9B-23  
5600 Fishers Lane  
Rockville, Maryland 20857-1706



ATTENTION: Robert Bedford, M.D.  
Acting Director

Re: NDA 20-478 Sevorane™ (sevoflurane)

Abbott Laboratories hereby amends the above-referenced New Drug Application to provide additional clinical and preclinical references. These references are new references that have been identified since the filing of the New Drug Application (NDA). The Table of Contents included in these volumes is a cumulative listing of all literature references i.e., those included in the original application and in this amendment. The new references that are included as part of this amendment are identified in the Table of Contents with an asterisk (\*).

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson  
Director,  
Regulatory Affairs  
Hospital Products Division  
(708) 937-3213

DTG/dg  
attachment  
12-94fda dtg

Question:

5. Describe if an alternate synthesis is used.

Response:

5. Sevoflurane is only manufactured and supplied to the customers according to the manufacturing process described in the DMF. When the manufacturing method may be revised, improved or changed, such process will be fully validated prior to be used or will be pre-inspected.

5. Comment:

Response acceptable

In regard to the stability data submitted, the following questions need to be answered:

Question:

6. The data appears to be within specification. However, the specification limits for total impurity, Compound A and Other single impurity are wide. Explain:

Either show the quality of the bulk substance at these wide ranges or reduce your specification limits to more realistic values.

Response:

6. The specifications for bulk sevoflurane were developed based on a review of the specifications currently in effect for marketed products of the same pharmacological, and the statistical review of the historical specification data available for development lots, and toxicological properties of the potential impurities that may be found in this product.

When more data are obtained with the production of consecutive lots of bulk drug at the new plant, annual review of specification performance will be performed in compliance with CGMP regulations and the DMF submission will be updated accordingly, as necessary.

COMMENT:

6. Firms are very reluctant to revise specification limits to more realistic values, however, as the firm gains more experience with the product and production lots are monitored and we evaluate stability data in annual reports, then we can have a better basis for holding them accountable.

Question:

7. The use of the word, "Pass" is not acceptable when a definite number has been determined. (Example: -

Response:

7. "Pass" means NMT the specification limit. For example, on page 122 (Table VI-1)

7. Comment:

I'll accept his response for now.

8. Define the actual number for Ambient Temperature in your tables.
9. Qualify the batches that are used as to pilot, research, or production and indicate in the Tables and indicate their date of manufacture and date put on stability.

Response:

8 and 9 : Table VI-1, VI-2, VI-3, VI-4, VI-5 and VI-6 were revised as attached. Actual temperature of ambient temperature is 0 to 35°C at the plant site area. Manufacturing date and starting date of stability study indicated were also shown in the tables.

All lots used for stability test were manufactured for production.

8. and 9.

Comment: response acceptable

"In your amendment dated January 5, 1995 the following question was asked and the following response was given. However, submit the information requested under my comment:

Request: "3. In regard to the filling process, what in-process controls are applied to assure that the air used to blow-out empty 250 mL bottles is acceptable and what in-process controls are applied to assure that the bulk drug prior to filling is properly filtered. Identify the particles or organism that may be present.

What evidence do you have that this product does not support growth? We call your attention to the fact that the agency is in the process of writing regulations that require liquid anesthetics to be sterile."

Response: Pharmacopoeia specified microbial inhibition tests have been performed with the required types and concentrations of bacterial and fungi strains (i.e., Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, Aspergillus niger and Candida albicans). Both vegetative and spore cell forms were used in these tests. These tests reveal that sevoflurane meets the requirements for classification as a microbial inhibition agent. Sevoflurane contact with these microorganisms resulted in 94 - 100% destruction of high level inoculum populations, within 24 - 144 hours of contact time.

COMMENT:

(A)

"We are requesting that data be submitted which show that Sevoflurane meets the requirements to be classified as a microbial inhibition agent."

Response:

The firm responded with microbial data and an explanation of the testing that was performed. ( see amendment for more details)  
However, see attached sheet for some of the conclusions reached.  
For the present time response is acceptable.

B. "When it was requested that physical and chemical properties of be submitted, I wanted data under such properties as described below for sevoflurane: ...."

#### 4.2.3 Physical and Chemical Characteristics

	<u>Sevoflurane</u>	<u>Compound A</u>
<u>Boiling Point at 760 mm Hg:</u>	58.6 °C	
<u>Specific Gravity at 20 °C:</u>	1.520 - 1.525	
<u>Vapor Density (air = 1.0g/L):</u>	6.9 g/L*	
<u>Vapor Pressure in mm Hg:</u>	157 mm Hg at 20 °C 197 mm Hg at 25 °C 317 mm Hg at 36 °C	

\* The vapor density was calculated based on the molecular weights of *Sevoflurane* (200.05) and air (28.8).

#### Distribution Partition Coefficients at 37 °C:

Blood/Gas  
Water/Gas  
Lard Fat/Gas  
Olive Oil/Gas

#### Main Component/Gas Partition Coefficients at 25 °C:

Conductive rubber  
Butyl rubber  
Polyvinyl chloride (endotracheal tube)  
Polyethylene (circuit tube)

#### Solubility

*Sevoflurane* is miscible with ethanol, ether, chloroform and petroleum benzene and it is slightly soluble in water.

#### Flammability

Response: For the present time the response is acceptable. ( see attached sheet for Compound A data)

C. "In the future, when stability data is reported, it is suggested that the chemical name of Compound A be cited in the Stability Report Table. The term 'Compound A' can be parenthesized."

Response: - We have informed the appropriate individuals to request that future stability data utilized the chemical name of Compound A.

Response acceptable.

4 pages

PURGED



Hospital Products Division

Abbott Laboratories  
D-389, Bldg. AF30  
200 Abbott Park Road  
Abbott Park, Illinois 60064-3537

December 21, 1994

CENTER FOR DRUG EVALUATION AND RESEARCH  
PILOT DRUG EVALUATION STAFF, HFD #007  
Attn: DOCUMENT CONTROL ROOM #9B-23  
5600 Fishers Lane  
Rockville, Maryland 20857-1706

ATTENTION: Robert Bedford, M.D.  
Acting Director

Re: NDA 20-478 Sevorane™ (sevoflurane)

Abbott Laboratories hereby amends the above-referenced New Drug Application to provide for additional revisions to the revised package insert that was submitted to the NDA on December 8, 1994. The submission of December 8, incorporated revisions and new information requested by the Division in their review of our proposed package insert included in the Original New Drug Application (NDA).

The enclosed package insert has been modified to include editorial comments that were offered by an Abbott-formed Advisory Panel. Accordingly, included herein is a revised package insert, as well as, an annotated insert which identifies the panel's recommendations. These changes are identified in the package insert by bold-underlined print. Also included herein are computer disks (in duplicate) in Word Perfect and MAC format.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson  
Director,  
Regulatory Affairs  
Hospital Products Division  
(708) 937-3213



DTG/dg  
attachment  
12-94fda.dtg



Hospital Products Division

Abbott Laboratories  
D-389, Bldg. AP30  
200 Abbott Park Road  
Abbott Park, Illinois 60064-3537

December 21, 1994

CENTER FOR DRUG EVALUATION AND RESEARCH  
PILOT DRUG EVALUATION STAFF, HFD #007  
Attn: DOCUMENT CONTROL ROOM #9B-23  
5600 Fishers Lane  
Rockville, Maryland 20857-1706



ATTENTION: Robert Bedford, M.D.  
Acting Director

Re: NDA 20-478 Sevorane™ (sevoflurane)

Abbott Laboratories hereby amends the above-referenced New Drug Application as a result of the Administration's position that the proposed product name, Sevorane™, is not consistent with USAN guidelines and therefore, should not be approved. Accordingly, we are proposing a new product name for sevoflurane namely, Ultane™. We would request that this name be presented to the Agency's labeling committee to deem its acceptability. Should you require any additional information, please contact me.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson  
Director,  
Regulatory Affairs  
Hospital Products Division  
(708) 937-3213

DTG/dg  
attachment  
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<p align="center"><b>DEPARTMENT OF HEALTH AND HUMAN SERVICES</b>  <b>PUBLIC HEALTH SERVICE</b>  <b>FOOD AND DRUG ADMINISTRATION</b></p> <p align="center"><b>APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE</b>  <b>OR AN ANTIBIOTIC DRUG FOR HUMAN USE</b>  <i>(Title 21, Code of Federal Regulations, 314)</i></p>		<p>Form Approved: OMB No. 0910-0001  Expiration Date: March 31, 1990.  See OMB Statement on Page 3.</p>	
		<b>FOR FDA USE ONLY</b>	
		DATE RECEIVED	DATE FILED
		DIVISION ASSIGNED-	NDA/ANDA NO. ASS-
NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).			
NAME OF APPLICANT Abbott Laboratories		DATE OF SUBMISSION December 21, 1994	
ADDRESS (Number, Street, City, State, and Zip Code) Hospital Products Division - DIV 2681 (D-389) 200 Abbott Park Road Abbott Park, IL 60064		TELEPHONE NO. (Include Area Code) (708) 937-5213	
		NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued) 20-478	
<b>DRUG PRODUCT</b>			
ESTABLISHED NAME (e.g., USPIUSAN)  N/A		PROPRIETARY NAME (If any)  Sevorane <sup>TM</sup>	
CODE NAME (If any)  Sevoflurane	CHEMICAL NAME  fluoromethyl-2,2,2-trifluoro-1-(trifluoro-methyl) ethyl ether		
DOSAGE FORM  Liquid	ROUTE OF ADMINISTRATION  Inhalation	STRENGTH(S)  N/A	
PROPOSED INDICATIONS FOR USE  Induction and maintenance of anesthesia.			
LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATION:			
<b>INFORMATION ON APPLICATION</b>			
TYPE OF APPLICATION (Check one)			
<input type="checkbox"/> THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) <input type="checkbox"/> THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)			
IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION			
NAME OF DRUG		HOLDER OF APPROVED APPLICATION	
STATUS OF APPLICATION (Check one)			
<input checked="" type="checkbox"/> PRESUBMISSION <input type="checkbox"/> AN AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> SUPPLEMENTAL APPLICATION <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> RESUBMISSION			
PROPOSED MARKETING STATUS (Check one)			
<input checked="" type="checkbox"/> APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) <input type="checkbox"/> APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)			

**CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
<input type="checkbox"/>	4. a. Samples (21 CFR 314.50 (e) (1)) (Subunit only upon FDA's request)
<input type="checkbox"/>	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
<input checked="" type="checkbox"/>	c. Labeling (21 CFR 314.50 (e) (2) (ii))
<input type="checkbox"/>	i. draft labeling (4 copies)
<input type="checkbox"/>	ii. final printed labeling (12 copies)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
<input type="checkbox"/>	7. Microbiology section (21 CFR 314.50 (d) (4))
<input type="checkbox"/>	8. Clinical data section (21 CFR 314.50 (d) (5))
<input type="checkbox"/>	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
<input type="checkbox"/>	10. Statistical section (21 CFR 314.50 (d) (6))
<input type="checkbox"/>	11. Case report tabulations (21 CFR 314.50 (f) (1))
<input type="checkbox"/>	12. Case reports forms (21 CFR 314.50 (f) (1))
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
<input type="checkbox"/>	15. OTHER (Specify)

Proposed Product Name

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211
2. Labeling regulations in 21 CFR 201
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72
5. Regulations on reports in 21 CFR 314.80 and 314.81
6. Local, state and federal environmental impact laws

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT Frederick A. Gustafson	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Frederick A. Gustafson</i>	DATE 12/21/94
ADDRESS (Street, City, State, Zip Code) One Abbott Park Rd Abbott Park, Illinois 60064		TELEPHONE NO (Include Area Code) (708) 937-3213

**(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)**

5 pages

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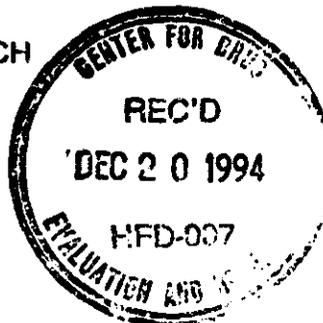
**Hospital Products Division**

Abbott Laboratories  
D-399, Bldg. AP30  
200 Abbott Park Road  
Abbott Park, Illinois 60064-3537

December 16, 1994

NO ATTACHMENT

CENTER FOR DRUG EVALUATION AND RESEARCH  
PILOT DRUG EVALUATION STAFF, HFD #007  
Attn: DOCUMENT CONTROL ROOM #9B-23  
5600 Fishers Lane  
Rockville, Maryland 20857-1706



ATTENTION: Robert Bedford, M.D.  
Acting Director

Re: NDA 20-478 Sevorane™ (sevoflurane)

Abbott Laboratories hereby amends the above-referenced New Drug Application to provide additional information requested in the December 15, 1994 FAX from Ms. Juanita Ross of the Division. Included herein is a copy of patents 2,992,276, 3,683,071 and 3,683,092. At the request of Ms. Ross, these copies have been previously FAX'ed to Dr. Pramoda Maturu of the Division.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson  
Director,  
Regulatory Affairs  
Hospital Products Division  
(708) 937-3213

DTG/dg  
attachment  
12-94/da.dtg

**ABBOTT**

DUPLICATE

Hospital Products Division

Abbott Laboratories  
D-389, Bldg. AP30  
200 Abbott Park F  
Abbott Park, Illin

ORIG AMENDMENT

December 7, *NOM*

CENTER FOR DRUG EVALUATION AND RESEARCH  
PILOT DRUG EVALUATION STAFF, HFD #007  
Attn: DOCUMENT CONTROL ROOM #9B-23  
5600 Fishers Lane  
Rockville, Maryland 20857-1706

ATTENTION: Robert Bedford, M.D.  
Acting Director

Re: NDA 20-478 Sevorane™ (sevoflurane)

Abbott Laboratories hereby amends the subject New Drug Application (NDA) to provide the clinical summary report for Sevoflurane protocol SEVO-92-025. The subject protocol SEVO-92-025 entitled: "A Phase III, Multi Center, Randomized, Open-Label Study comparing sevoflurane to isoflurane in the maintenance of anesthesia and rapidity and ease of emergence and recovery in adult ASA Class I, II, or III inpatients", was submitted to the IND on January 19, 1993.

The study summary is contained in four (4) volumes. The Full Clinical Summary, as well as, the individual Appendices where appropriate, include a Table of Contents to locate specific pages within that section. Preceding the Full Clinical Summary is the completed Abbreviated Summary and associated computer disk (Microsoft Word format). Also included as part of this submission is a data disk for the datasets included in this clinical study report.

We trust that this information is complete.

Sincerely,

ABBOTT LABORATORIES

*Frederick A. Gustafson*

Frederick A. Gustafson  
Director, Regulatory Affairs  
Hospital Products Division  
Phone: (708) 937-3213  
Fax: (708) 938-7867

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November 30, 1994 Food and Drug Administration  
Rockville MD 20857

Frederick A. Gustafson  
Director, Regulatory Affairs  
Hospital Products Division  
Abbott Laboratories  
D-386, Bldg. AP30  
200 Abbott Park Road  
Abbott Park, Illinois 60064-3637

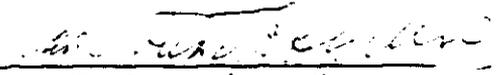
Re: NDA 20-478 Sevoflurane

Dear Mr. Gustafson:

This is in response to your letter of November 29, 1994, concerning the January 17-18, 1995 meeting of the Anesthetic and Life Support Drugs Advisory Committee. In that letter you request that the Advisory Committee meeting be structured to allow for both open and closed sessions and that information and discussions relating to the pending application be restricted to a closed session.

In response, I refer you to 21 CFR 314.430 (c) and (d) and 21 CFR 14.35 (c). If your organization has never publicly disclosed or acknowledged the existence of its application for sevoflurane, then our regulations preclude us from disclosing safety and effectiveness data at an open session of an FDA advisory committee. Hence, we would conduct all discussions of your pending application in a closed session. If, however, you have disclosed or acknowledged the existence of your application, it is FDA policy that the safety and effectiveness issues for your application are to be discussed in an open session of an FDA advisory committee and that issues concerning chemistry and manufacturing are to be discussed in a closed session.

Thus, the answer to your request depends on whether Abbott has ever publicly disclosed or acknowledged the existence of its application for sevoflurane. It would be my presumption that Abbott has publicly disclosed or acknowledged the existence of its application and that the discussion of the safety and effectiveness issues will take place in an open session. If this is not correct, please contact me today if possible, so that I can meet the deadline for the Federal Register notice. Further, it is now my understanding there may be chemistry or manufacturing discussion before the committee, so we are including a closed session for one hour for this purpose and the rest of the meeting will be conducted in open session.

  
Isaac F. Roubein, Ph.D.  
Executive Secretary

Attachment

not readily available from the members of the committee. Consultants may be either from outside the Government or from agencies other than the Food and Drug Administration. Reports, data, information, and other written submissions made to a public advisory committee by a consultant are part of the administrative record itemized in § 14.70

(44 FR 22351, Apr. 13, 1979, as amended at 55 FR 42703, Oct. 23, 1990)

**§ 14.33 Compilation of materials for members of an advisory committee.**

The Commissioner shall prepare and provide to all committee members a compilation of materials bearing upon members' duties and responsibilities, including:

- (a) All applicable conflict of interest laws and regulations and a summary of their principal provisions;
- (b) All applicable laws and regulations relating to trade secrets and confidential commercial or financial information that may not be disclosed publicly and a summary of their principal provisions;
- (c) All applicable laws, regulations, and guidelines relating to the subject matter covered by the advisory committee and a summary of their principal provisions;
- (d) All applicable laws, regulations, including the regulations in part 20 of this chapter, advisory committee charters, FEDERAL REGISTER notices, curricula vitae, rules adopted by the advisory committee, and other material relating to the formation, composition, and operation of the advisory committee, and a summary of their principal provisions;
- (e) Instructions on whom to contact when questions arise; and
- (f) Other material relating to FDA and the subject matter covered by the committee which may facilitate the work of the committee.

**§ 14.35 Written submissions to an advisory committee.**

(a) Ten copies of written submissions to a committee are to be sent to the executive secretary unless an applicable FEDERAL REGISTER notice or other regulations in this chapter specify otherwise. Submissions are subject to the

provisions of § 10.20, except that it is not necessary to send copies to the Dockets Management Branch.

(b) At the request of a committee, or on the Commissioner's own initiative, the Commissioner may issue in the FEDERAL REGISTER a notice requesting the submission to the committee of written information and views pertinent to a matter being reviewed by the committee. The notice may specify the manner in which the submission should be made.

(c) At the request of a committee, or on the Commissioner's own initiative, the Commissioner may at any time request the applicant or sponsor of an application or petition about a specific product on which action is pending before FDA, and is being reviewed by an advisory committee, to present or discuss safety, effectiveness, or other data concerning the product during a regularly scheduled meeting of the committee. The request may be for an oral presentation or for a concise, well-organized written summary of pertinent information for review by the committee members before the meeting, or both. Unless specified otherwise, one copy of the written summary along with a proposed agenda outlining the topics to be covered and identifying the participating industry staff members or consultants that will present each topic is to be submitted to the executive secretary or other designated agency employee at least 30 days before the meeting.

(d) An interested person may submit to a committee written information or views on any matter being reviewed. Voluminous data is to be accompanied by a summary. A submission is to be made to the executive secretary and not directly to a committee member.

(1) FDA will distribute submissions to each member, either by mail or at the next meeting. Submissions will be considered by the committee in its review of the matter.

(2) A committee may establish, and give public notice of, a cutoff date after which submissions about a matter will no longer be received or considered.

(e) The Commissioner will provide the committee all information the Commissioner deems relevant. A mem-

ber will, upon request, also be provided any material available to FDA which the member believes appropriate for an independent judgment on the matter, e.g., raw data underlying a summary or report, or a briefing on the legal aspects of the matter.

**§ 14.39 Additional rules for a particular advisory committee.**

(a) In addition to these rules, an advisory committee may, with the concurrence of the designated Federal employees, adopt additional rules which are not inconsistent with this subpart or with other legal requirements.

(b) Any additional rules will be included in the minutes of the meeting when adopted and in the materials compiled under § 14.33 and will be available for public disclosure under § 14.65(c).

**Subpart C—Establishment of Advisory Committees**

**§ 14.40 Establishment and renewal of advisory committees.**

(a) An advisory committee may be established or renewed whenever it is necessary or appropriate for the committee to hold a public hearing and to review and make recommendations on any matter pending before FDA. Except for committees established by statute, before a committee is established or renewed it must first be approved by the Department pursuant to 45 CFR part 11 and by the General Services Administration.

(b) When an advisory committee is established or renewed, the Commissioner will issue a FEDERAL REGISTER notice certifying that the establishment and renewal is in the public interest and stating the structure, function, and purposes of the committee and, if it is a standing advisory committee, shall amend § 14.100 to add it to the list of standing advisory committees. A notice of establishment will be published at least 15 days before the filing of the advisory committee charter under paragraph (c) of this section. A notice of renewal does not require the 15-day notice.

(c) No committee may meet or take action until its charter is prepared and filed as required by section 9(c) of the

incorporate. If the holder restricts the authorization to particular drug products, the list is required to include the name of each drug product and the application number, if known, to which the authorization applies.

(e) The public availability of data and information in a drug master file, including the availability of data and information in the file to a person authorized to reference the file, is determined under part 20 and § 314.430.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910-0001) (50 FR 7493, Feb. 22, 1985, as amended at 50 FR 21234, May 23, 1985, 53 FR 33122, Aug. 30, 1988, 55 FR 28380, July 11, 1990)

**§ 314.430 Availability for public disclosure of data and information in an application or abbreviated application.**

(a) The Food and Drug Administration will determine the public availability of any part of an application or abbreviated application under this section and part 20 of this chapter. For purposes of this section, the application or abbreviated application includes all data and information submitted with or incorporated by reference in the application or abbreviated application, including investigational new drug applications, drug master files under § 314.420, supplements submitted under § 314.70 or § 314.97, reports under § 314.80 or § 314.98, and other submissions. For purposes of this section, safety and effectiveness data include all studies and tests of a drug on animals and humans and all studies and tests of the drug for identity, stability, purity, potency, and bioavailability.

(b) FDA will not publicly disclose the existence of an application or abbreviated application before an approvable letter is sent to the applicant under § 314.110, unless the existence of the application or abbreviated application has been previously publicly disclosed or acknowledged. The Center for Drug Evaluation and Research will maintain and make available for public disclosure a list of applications or abbreviated applications for which the agency has sent an approvable letter to the applicant.

(c) If the existence of an unapproved application or abbreviated application has not been publicly disclosed or acknowledged, no data or information in the application or abbreviated application is available for public disclosure.

(d) If the existence of an application or abbreviated application has been publicly disclosed or acknowledged before the agency sends an approval letter to the applicant, no data or information contained in the application or abbreviated application is available for public disclosure before the agency sends an approval letter, but the Commissioner may, in his or her discretion, disclose a summary of selected portions of the safety and effectiveness data that are appropriate for public consideration of a specific pending issue; for example, for consideration of an open session of an FDA advisory committee.

(e) After FDA sends an approval letter to the applicant, the following data and information in the application or abbreviated application are immediately available for public disclosure, unless the applicant shows that extraordinary circumstances exist. A list of approved applications and abbreviated applications, entitled "Approved Drug Products with Therapeutic Equivalence Evaluations," is available from the Government Printing Office, Washington, DC 20402. This list is updated monthly.

(1) (Reserved)

(2) If the application applies to a new drug, all safety and effectiveness data previously disclosed to the public as set forth in § 20.81 and a summary or summaries of the safety and effectiveness data and information submitted with or incorporated by reference in the application. The summaries do not constitute the full reports of investigations under section 505(b)(1) of the act (21 U.S.C. 355(b)(1)) on which the safety or effectiveness of the drug may be approved. The summaries consist of the following:

(1) For an application approved before July 1, 1975, internal agency records that describe safety and effectiveness data and information, for example, a summary of the basis for approval or internal reviews of the data

and information, after deletion of the following:

(a) Names and any information that would identify patients or test subjects or investigators.

(b) Any inappropriate gratuitous comments unnecessary to an objective analysis of the data and information.

(1) For an application approved on or after July 1, 1975, a Summary Basis of Approval (SBA) document that contains a summary of the safety and effectiveness data and information evaluated by FDA during the drug approval process. The SBA is prepared in one of the following ways:

(a) Before approval of the application, the applicant may prepare a draft SBA which the Center for Drug Evaluation and Research will review and may revise. The draft may be submitted with the application or as an amendment.

(b) The Center for Drug Evaluation and Research may prepare the SBA.

(3) A protocol for a test or study, unless it is shown to fall within the exemption established for trade secrets and confidential commercial information in § 20.61.

(4) Adverse reaction reports, product experience reports, consumer complaints, and other similar data and information after deletion of the following:

(1) Names and any information that would identify the person using the product.

(1) Names and any information that would identify any third party involved with the report, such as a physician or hospital or other institution.

(5) A list of all active ingredients and any inactive ingredients previously disclosed to the public as set forth in § 20.81.

(6) An assay method or other analytical method, unless it serves no regulatory or compliance purpose and is shown to fall within the exemption established for trade secrets and confidential commercial information in § 20.61.

(7) All correspondence and written summaries of oral discussions between FDA and the applicant relating to the application, under the provisions of Part 20.



Hospital Products Division

Abbott Laboratories  
D-380, Bldg. AP30  
200 Abbott Park Road  
Abbott Park, Illinois 60084-3537

ORIGINAL

NEW CORRESP

November 29, 1994

CENTER FOR DRUG EVALUATION AND RESEARCH  
PILOT DRUG EVALUATION STAFF, HFD #007  
Attn: DOCUMENT CONTROL ROOM #9B-23  
5600 Fishers Lane  
Rockville, Maryland 20857-1708



ATTENTION: Isaac F. Roubein, Ph.D  
Executive Secretary, Anesthetic and  
Life Support Drugs Advisory Committee

Re: NDA 20-478 Sevoflurane

Abbott Laboratories acknowledges receipt of the notification of the January 17-18, 1995 meeting of the Anesthetic and Life Support Drugs Advisory Committee to discuss the subject pending New Drug Application (NDA).

Abbott Laboratories requests that this Advisory Panel meeting be structured to allow for both open and closed sessions. Since this NDA is pending, information contained in this application, as well as the Agency reviews, are not releasable to the general public. Accordingly, Abbott Laboratories requests that information and discussions relating to the pending application be restricted to a closed Advisory Panel session, thereby assuring the confidentiality of this information.

Sincerely,

ABBOTT LABORATORIES

*Frederick A. Gustafson*

Frederick A. Gustafson  
Director, Regulatory Affairs  
Hospital Products Division  
Phone: (708) 937-3213  
Fax: (708) 938-7867

*Request received -  
This matter is being  
discussed between  
the Sponsor & John Tracy,  
Director of Advisors & Compliance Staff  
R Bedford  
12/20/94*

DTG/dg  
G:\dtg\11-94\da.dtg

NDA 20-478

Abbott Hospital Products Division  
Abbott Laboratories  
One Abbott Park Road  
Abbott Park, Illinois 60064-3500

OCT 21 1994

Attention: Frederick A. Gustafson  
Director, Regulatory Affairs  
Hospital Products Division

Dear Mr. Gustafson:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sevoflurane (sevoflurane) liquid anesthetic for general anesthesia.

We have completed our review of the environmental impact analysis section of your submission, and have identified the following deficiencies:

1. For item #4, please provide the environment surrounding each of the production, distribution and disposal sites. Provide the estimated amount of use in kg/lbs/liter per year. Specify the amount of the drug substance that would be disposed as unused drug product per year on the fifth year of production. Provide the address and environment surrounding the site where recovery and disposal of the returned goods would be made.
2. For item #5, please provide the structure and physicochemical properties impurities (if any) in this section. Provide a better copy of the material safety data sheet for the drug substance.
3. For item # 6, please provide estimated emission of the drug substance and other materials related to the synthesis of sevoflurane from the Facility per year on the fifth year of production. State what type of control would be taken to minimize emission. Provide state, local and federal environmental compliance letter issued to the specific to the product. Include a certified copy of the English version. Also provide product specific compliance letter from the appropriate local, state and federal authorities for the air and water emission of sevoflurane from

Page Two  
NDA 20-478

the Rocky Mountain Plant and for the site of disposal of returned and off-specification product. Provide estimated amount of returned and off-specification product per year for the fifth year of production in this section also. Also provide information on MEEC data in this item of the environmental assessment.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions concerning this NDA, please contact Ms. Leslie Vaccari, Project Manager at (301) 443-3741

Sincerely yours,

Asoke Mukherjee, Ph.D.  
Pharmacologist  
Pilot Drug Evaluation Staff, HFD-007  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**ABBOTT**

**Hospital Products Division**

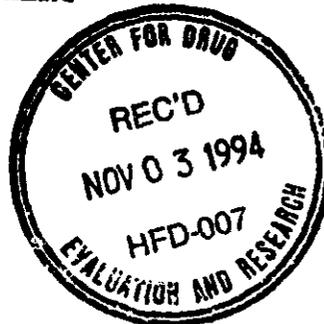
Abbott Laboratories  
D-388, Bldg. AP30  
200 Abbott Park Road  
Abbott Park, Illinois 60064-3537

DUPLICATE

ORIG AMENDMENT

October 28, 1994

*N (3M)*



CENTER FOR DRUG EVALUATION AND RESEARCH  
PILOT DRUG EVALUATION STAFF, HFD #007  
Attn: DOCUMENT CONTROL ROOM #9B-23  
5600 Fishers Lane  
Rockville, Maryland 20857-1706

ATTENTION: Robert Bedford, M.D.  
Acting Director

Re: NDA 20-478 Sevorane™ (sevoflurane)

Abbott Laboratories hereby amends the subject New Drug Application (NDA) to provide the clinical summary report for Sevoflurane protocol SEVO-93-042. The subject protocol SEVO-93-042 entitled: "A Phase I, Single Center, Open-Label Study Evaluating the Effect of Sevoflurane on Autonomic Nervous System in Healthy Male Volunteers" was submitted to the IND on November 8, 1993.

The study summary is contained in two (2) volumes. The Full Clinical Summary, as well as, the individual Appendices where appropriate, include a Table of Contents to locate specific pages within that section. Preceding the Full Clinical Summary is the completed Abbreviated Summary and associated computer disk (Microsoft Word format). Also included as part of this submission is a data disk for the datasets included in this clinical study report.

We trust that this information is complete.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson  
Director, Regulatory Affairs  
Hospital Products Division  
Phone: (708) 937-3213  
Fax: (708) 938-7867

*Reviewer's copy  
shipped to R. Merin, M.D.  
for review.*

DTG/dg  
attachment  
G:\dtg\10-94fda.dtg



Hospital Products Division

Abbott Laboratories  
One Abbott Park Road  
Abbott Park, Illinois 60064-3500

October 28, 1994

Dr. Robert Merin  
Department of Anesthesiology - B1W 2144  
Medical College of Georgia  
1120 15th Street  
Augusta, GA 30912 - 2700



Attn: Dr. Merin:

Re: Sevorane™ (sevoflurane)  
NDA 20-478

At the request of the Pilot Drug Division, the following documents are being provided to you for your review in support of the above-referenced NDA:

1. Complete Study Report for the following clinical study:

<u>Study Category</u>	<u>Study Number</u>	<u>Protocol No.</u>
Cardiac	29A	SEVO-93-042

2. Individual Study Summary (paper copy)
3. Individual Study Summary (Microsoft Word Disk)

A copy of the proposed draft package insert (paper copy and computer disk) have been previously provided to you on July 27, 1994 in the initial submission of final study reports.



Page Two  
October 28, 1994

If you have any questions or experience any problems with the supplied computer disks, please contact me. Following the completion of your review and/or approval of the New Drug Application, we ask that you destroy these documents in a manner that will maintain their confidentiality.

Sincerely,

ABBOTT LABORATORIES

David T. Guzek  
Director,  
Regulatory Administration  
Hospital Products Division  
(708) 937-3216

DTG/dg  
attachment

cc: Dr. Robert Bedford HFD #007  
Ms. Leslie Vacari HFD #007



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

October 31, 1994

Dr. Frederick A. Gustafson  
Director, Regulatory Affairs  
Abbott Laboratories  
One Abbott Park  
Abbott Park, Illinois 60064-3500

Dear Dr Gustafson:

This is to inform you that your product "Sevoflurane," NDA 20-478, will be brought before the Anesthetic and Life Support Drugs Advisory Committee at the meeting of January 17-18, 1995.

Sevoflurane will be discussed in open session except for parts of the chemistry, manufacturing, and/or other matters, involving confidential or trade secret information, which will be discussed in closed session.

Should you have any questions please call me at 301/443-5455.

Sincerely,

Isaac F. Roubein, Ph.D.  
Executive Secretary, Anesthetic,  
and Life Support Drugs  
Advisory Committee



NDA 20-478

Hospital Products Division  
Abbott Laboratories  
One Abbott Park Road  
Abbott Park, Illinois 60064-3500

AUG 12 1994

Attention: Frederick A. Gustafson  
Director, Regulatory Affairs  
Hospital Products Division

Dear Mr. Gustafson:

We have received your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Sevorane (sevoflurane)  
Liquid anesthetic for general anesthesia  
250 mL

Therapeutic Classification: S

Date of Application: July 8, 1994

Date of Receipt: July 11, 1994

Our Reference Number: NDA 20-478

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 9, 1994 in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations and in accordance with the policy described in the Center for Drug Evaluation and Research Staff Manual Guide CDER 4820.6, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact me at (301) 443-3741.

**NDA 20-478  
Page Two**

**Please cite the NDA number listed above at the top of the first page of any communications concerning this application.**

**Sincerely yours,,**

**Leslie Vaccari  
Project Manager  
Pilot Drug Evaluation Staff  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research**



Hospital Products Division

Abbott Laboratories  
One Abbott Park Road  
Abbott Park, Illinois 60064-3500

ORIGINAL

*N (BM)*

July 27, 1994

CENTER FOR DRUG EVALUATION AND RESEARCH  
PILOT DRUG EVALUATION STAFF, HFD #007  
Attn: DOCUMENT CONTROL ROOM #9B-23  
5600 Fishers Lane  
Rockville, Maryland 20857-1706

ATTENTION: Robert Bedford, M.D.  
Acting Director

Re: Sevorane™ (sevoflurane)  
NDA 20-478

The following documents are being provided to you for your review in support of the above-referenced NDA:

1. Individual Study Summary (paper copy)

<u>Study Category</u>	<u>Study Number</u>	<u>Protocol No.</u>
Neurosurgery	36	528
	37	SEVO-92-017
	38	SEVO-92-035

2. Individual Study Summary (Microsoft Word Disk)
3. Draft Package Insert (paper copy)
4. Draft Package Insert (Microsoft Word Disk)

If you have any questions or experience any problems with the supplied computer disks, please contact me.

Sincerely,

ABBOTT LABORATORIES

David T. Guzek  
Director,  
Regulatory Administration  
Hospital Products Division  
(708) 937-3216



Hospital Products Division

Abbott Laboratories

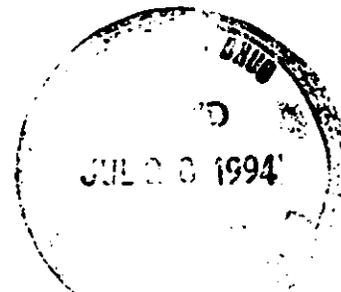
One Abbott Park Road

Abbott Park, Illinois 60064-3500

**ORIGINAL**

July 27, 1994

Dr. Margaret Wood  
Department of Anesthesiology  
Vanderbilt University School of Medicine  
2301 TVC  
Nashville, TN 37232



Re: Sevorane™ (sevoflurane)  
NDA 20-478

At the request of the Pilot Drug Division, the following documents are being provided to you for your review in support of the above-referenced NDA:

1. Complete Study Reports for the following clinical studies:

<u>Study Category</u>	<u>Study Number</u>	<u>Protocol No.</u>
Pediatric	1	532
	21	SEVO-92-007
	22	SEVO-92-001
	23	SEVO-92-008
	24	533
	25	534

2. Individual Study Summary (paper copy)
3. Individual Study Summary (Microsoft Word Disk)
4. Draft Package Insert (paper copy)
5. Draft Package Insert (Microsoft Word Disk)

# ABBOTT

Hospital Products Division

Abbott Laboratories  
One Abbott Park Road  
Abbott Park, Illinois 60064-3500

~~NEW CORRESP~~

ORIGINAL

July 27, 1994

Dr. C. Philip Larson, Jr.  
Department of Anesthesiology  
UCLA School of Medicine  
924 West Wood Blvd.  
Suite 335  
Los Angeles, CA 90024



Attn: Dr. Larson:

Re: Sevorane™ (sevoflurane)  
NDA 20-478

At the request of the Pilot Drug Division, the following documents are being provided to you for your review in support of the above-referenced NDA:

1. Complete Study Reports for the following clinical studies:

<u>Study Category</u>	<u>Study Number</u>	<u>Protocol No.</u>
Adult	2	SEVO-92-034
	10	SEVO-92-003
	11	SEVO-92-009
	12	SEVO-92-004
	13	-520
	14	524
	15	525
	16	SEVO-92-005
	17	SEVO-92-006A
	18	SEVO-92-025
	19	-526
20	SEVO-92-006	

2. Individual Study Summary (paper copy)
3. Individual Study Summary (Microsoft Word Disk)
4. Draft Package Insert (paper copy)
5. Draft Package Insert (Microsoft Word Disk)

# ABBOTT

Hospital Products Division

Abbott Laboratories

One Abbott Park Road

Abbott Park, Illinois 60064-3500

July 27, 1994

ORIGINAL  
SUPPL NEW CORRESP

Dr. Renee Landesman  
11073 Gaither Farm Road  
Ellicott City, MD 21042



Attn: Dr. Landesman:

Re: Sevorane™ (sevoflurane)  
NDA 20-478

At the request of the Pilot Drug Division, the following documents are being provided to you for your review in support of the above-referenced NDA:

1. Complete Study Reports for the following clinical studies:

<u>Study Category</u>	<u>Study Number</u>	<u>Protocol No.</u>
Metabolism/ Safety	3	SEVO-93-037
	4	SEVO-93-039
	5	SEVO-92-014
	6	-522
	7	SEVO-93-040
	8	-531
	9	SEVO-92-015

2. Individual Study Summary (paper copy)
3. Individual Study Summary (Microsoft Word Disk)
4. Draft Package Insert (paper copy)
5. Draft Package Insert (Microsoft Word Disk)

# ABBOTT

Hospital Products Division

Abbott Laboratories

One Abbott Park Road

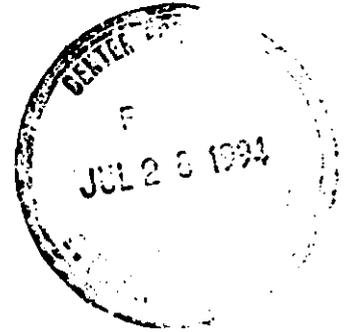
Abbott Park, Illinois 60064-3500

ORIGINAL

~~SUPPL~~ NEW CORRESP

July 27, 1994

Dr. Robert Merin  
Department of Anesthesiology - B1W 2144  
Medical College of Georgia  
1120 15th Street  
Augusta, GA 30912 - 2700



Attn: Dr. Merin:

Re: Sevorane™ (sevoflurane)  
NDA 20-478

At the request of the Pilot Drug Division, the following documents are being provided to you for your review in support of the above-referenced NDA:

1. Complete Study Reports for the following clinical studies:

<u>Study Category</u>	<u>Study Number</u>	<u>Protocol No.</u>
Cardiac	26	SEVO-92-010
	27	-535
	28	523
	29	SEVO-92-033

2. Individual Study Summary (paper copy)
3. Individual Study Summary (Microsoft Word Disk)
4. Draft Package Insert (paper copy)
5. Draft Package Insert (Microsoft Word Disk)

# ABBOTT

Hospital Products Division

Abbott Laboratories

One Abbott Park Road

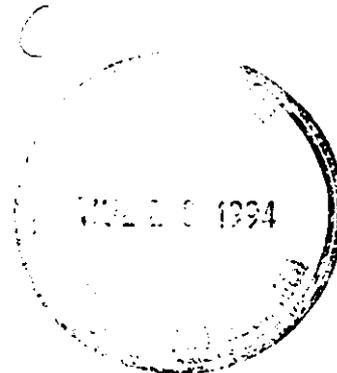
Abbott Park, Illinois 60064-3500

SUPPL NEW CORRESP

ORIGINAL

July 27, 1994

Dr. Marie Young  
Department of Anesthesia  
4th Floor/Ravdin Courtyard  
Room 408  
Hospital of the University of Pennsylvania  
3400 Spruce Street  
Philadelphia, PA 19104



Attn: Dr. Young:

Re: Sevorane™ (sevoflurane)  
NDA 20-478

At the request of the Pilot Drug Division, the following documents are being provided to you for your review in support of the above-referenced NDA:

1. Complete Study Reports for the following clinical studies:

<u>Study Category</u>	<u>Study Number</u>	<u>Protocol No.</u>
Renal/Hepatic/ Elderly	30	.536
	31	SEVO-92-002
	32	SEVO-92-012
	33	530
	34	529
	35	SEVO-93-044

2. Individual Study Summary (paper copy)
3. Individual Study Summary (Microsoft Word Disk)
4. Draft Package Insert (paper copy)
5. Draft Package Insert (Microsoft Word Disk)

**ABBOTT**

**SUPPL NEW CORRESP**

Hospital Products Division

Abbott Laboratories

One Abbott Park Road

Abbott Park, Illinois 60064-3500

ORIGINAL

July 27, 1994

Dr. James Eisenach  
457 Hutchinson Avenue  
Iowa City, Iowa 52240

Attn: Dr. Eisenach:

Re: Sevorane™ (sevoflurane)  
NDA 20-478



At the request of the Pilot Drug Division, the following documents are being provided to you for your review in support of the above-referenced NDA:

1. Complete Study Reports for the following clinical studies:

<u>Study Category</u>	<u>Study Number</u>	<u>Protocol No.</u>
OB/Muscle	39	SEVO-92-011
Relaxants	40	SEVO-92-013

2. Individual Study Summary (paper copy)
3. Individual Study Summary (Microsoft Word Disk)
4. Draft Package Insert (paper copy)
5. Draft Package Insert (Microsoft Word Disk)

If you have any questions or experience any problems with the supplied computer disks, please contact me. Following the completion of your review and/or approval of the New Drug Application, we ask that you destroy these documents in a manner that will maintain their confidentiality.

Sincerely,

ABBOTT LABORATORIES

A handwritten signature in cursive script, appearing to read "David T. Guzek".

David T. Guzek  
Director,  
Regulatory Administration  
Hospital Products Division  
(708) 937-3216



Food and Drug Administration  
Rockville MD 20857

NDA 20-478

Abbott Hospital Products Division  
Abbott Laboratories  
One Abbott Park Road  
Abbott Park, Illinois 60064-3500

MAY 13 1994

Attention: Frederick A. Gustafson  
Director, Regulatory Affairs  
Hospital Products Division

Dear Mr. Gustafson:

We have received your presubmission of chemistry, manufacturing and controls information for the following:

Name of Drug Product: Sevorane (Sevoflurane)

Date of Application: April 29, 1994

Date of Receipt: May 2, 1994

Our Reference Number: NDA 20-478

We will review this early submission as resources permit. We will not, however, consider it subject to the 180-day review time limit or to a filing decision by FDA. Should you have any questions regarding this information, please contact me at (301) 443-3741.

Our willingness to accept your pre-submission is based upon the condition that the full application will be submitted no sooner than 90 days nor later than 120 days from the date of your submission. If such submission is not within this time frame, the Agency may exercise its right to return the presubmission to you without further explanation or action.

Please cite the NDA number assigned to this application at the top of the first page of every communication concerning this application.

Sincerely yours,

Leslie Vaccari  
Project Manager  
Pilot Drug Evaluation Staff, HFD-007  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

NDA 20-478

Abbott Hospital Products Division  
Abbott Laboratories  
One Abbott Park Road  
Abbctt Park, Illinois 60064-3500



Attention: Frederick A. Gustafson  
Director, Regulatory Affairs  
Hospital Products Division

Dear Mr. Gustafson:

We have received your presubmission of chemistry, manufacturing and controls information for the following:

Name of Drug Product: Sevorane (Sevoflurane)

Date of Application: April 29, 1994

Date of Receipt: May 2, 1994

Our Reference Number: NDA 20-478

We will review this early submission as resources permit. We will not, however, consider it subject to the 180-day review time limit or to a filing decision by FDA. Should you have any questions regarding this information, please contact me at (301) 443-3741.

Our willingness to accept your pre-submission is based upon the condition that the full application will be submitted no sooner than 90 days nor later than 120 days from the date of your submission. If such submission is not within this time frame, the Agency may exercise its right to return the presubmission to you without further explanation or action.

Please cite the NDA number assigned to this application at the top of the first page of every communication concerning this application.

Sincerely yours,

Leslie Vaccari  
Project Manager  
Pilot Drug Evaluation Staff, HFD-007  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

**Hospital Products Division**

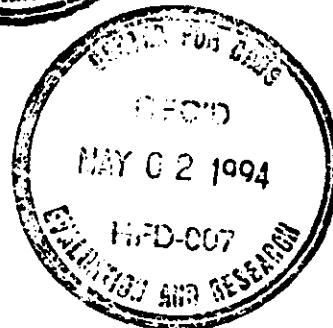
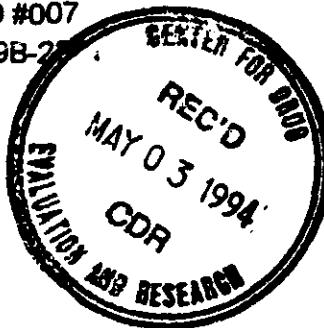
Abbott Laboratories  
 One Abbott Park Road  
 Abbott Park, Illinois 60064-3500

April 29, 1994

CENTER FOR DRUG EVALUATION AND RESEARCH  
 PILOT DRUG EVALUATION STAFF, HFD #007  
 Attn: DOCUMENT CONTROL ROOM #9B-25  
 5600 Fishers Lane  
 Rockville, Maryland 20857-1706

ATTENTION: Curtis Wright, M.D.  
 Acting Director

Re: Sevorane™ (Sevoflurane)  
 NDA 20-478



Abbott Laboratories hereby pre-submits the Chemistry, Manufacturing and Controls (CMC) Section of the subject New Drug Application (NDA) for the Division's review per 21 CFR 314.50(d)(1)(iv).

The subject drug, Sevorane™ (Sevoflurane), is a liquid anesthetic intended for induction and maintenance of general anesthesia. The finished dosage form will be manufactured at Abbott Laboratories' Hospital Products Division, Rocky Mount, North Carolina production facility. The drug product will be supplied as follows:

<u>List No.</u>	<u>Product</u>	<u>Dosage Form</u>	<u>Size</u>
4456	Sevorane™ (Sevoflurane)	Liquid	250mL

As discussed and agreed upon in the March 8, 1994 FDA/Abbott pre-NDA meeting with Ms. Juanita Ross of the Division, the CMC section is being submitted prior to the submission of the Drug Master File by \_\_\_\_\_ for the manufacture of the bulk drug substance in its new manufacturing facility. This master file and the data to demonstrate the equivalency of the bulk drug manufactured in the current versus new facility will be submitted in July 1994. The new \_\_\_\_\_ manufacturing facility which is included in this application will be ready for a pre-approval inspection in August 1994. The Rocky Mount, North Carolina manufacturing site for the finished drug product is currently ready for a pre-approval inspection. Please refer to the accompanying Table of Contents for a list of the data supporting this submission.

Curtis Wright, M.D.

Page Two

April 29, 1994

As required by Section 314.50(d)(3) of the Final Rule, published in the Federal Register, September 8, 1993, page 47351, "The applicant shall submit a field copy of the application that contains the technical section ..... and a certification that the field copy is a true copy of the technical section ..... contained in the archival and review copies of the application." As required, this field copy will be submitted and certification made at the time of the full archival NDA submission.

Please direct any inquiries regarding this pre-submission to Mr. David Guzek at (301) 937-3216.

We trust that this information is complete.

Sincerely,

ABBOTT LABORATORIES



Frederick A. Gustafson  
Director, Regulatory Affairs  
Hospital Products Division  
Phone: (708) 937-3213  
Fax: (708) 938-7867

DTG/dg  
attachment  
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NDA 20-478

Food and Drug Administration  
Rockville MD 20857

Abbott  
Hospital Products Division  
Abbott Laboratories  
One Abbott Park Road  
Abbott Park, Illinois 60064-3500.

DEC 23 1994

Attention: Frederick A. Gustafson  
Director, Regulatory Affairs  
Hospital Products Division

Dear Mr. Gustafson:

Please refer to your pending July 11, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Sevorane (sevoflurane) liquid anesthetic for general anesthesia 250 mL.

We have completed our review of the Chemistry section of your submission and have identified the following deficiencies:

1. On pages 239-244, data was submitted for 36 lots of bulk drug manufactured in Japan tested as per current test batch methods.

Batches:

# C-1,2,3,5,6,7,8,9,10,12,13,14,15,16,  
17,18,19,20,21,23,24,25,26,27,28  
#71104, #00210, #11224, #1120061

- a.) Clarify the absence of such information as:
  - Date these batches were manufactured
  - Date these batches were tested
  - Explain the batch numbering system.
- b.) For all the above batches clarify the absence of the following data:
  - Refractive Index
  - Identification (IR)/include copies of spectra
  - Fluoride Ions
  - Largest Single impurity
  - Acidity/Alkalinity - the word "Pass" is not acceptable, include actual data.
- c.) Include the chemical names of Compound A, Largest Single Impurity and any of the known Total Impurities in your Tables.
- d.) On pages 239 to 243, some of the values for Largest Total Impurities as out of specification limits. Please explain.

2. Submit a Certificate of Analysis of your reference standard showing its quality as compared to the testing of Sevoflurane in the Table below.

Table IV Specifications for Sevoflurane		
Test	STMe	Specifications


3. In regard to the filling process, what in-process controls are applied to assure that the air used to blow-out empty 250 mL bottles is acceptable and what in-process controls are applied to assure that the bulk drug prior to filling is properly filtered. Identify the particles or organism that may be present.

What evidence do you have that this product does not support growth? We call your attention to the fact that the agency is in the process of writing regulations that require liquid anesthetics to be sterile.

4. It is noted in the Table below, that at the end of six months "ALL" of the lots are reading much below the specification limits. Explain how your specification limits were derived and show the quality of your product at both extreme ranges for all tests indicated.

Table XXXXI Stability Data (continued) 250 mL Screw Cap Closure System (Reclaim Product)								
Test Performed	Fluoride	Acidity** or Alkalinity	Non- volatile Residues	Water Content	Total Imp. w/o Cpd. A	Cpd. A	Other Largest Imp.	Sevo Purity
Test Method Assignment:								
Final Specifications:								
Lot # / Stability #	Temp	Month/ Position	Results					

5. Clarify the revised specification in your stability protocol for Compound A in Appendix J, Page 492 of NMT

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Leslie Vaccari  
Consumer Safety Officer  
(301) 443-3741

Sincerely yours,

Juanita Ross  
Chemist  
Pilot Drug Evaluation Staff, HFD-007  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

SEVORANE

Sevoflurane

A review did not reveal names which sound or look like the proposed name.

The Committee noted the proposed name is composed of 3 of the 4 syllables of the established name. The Agency supports the spirit of USAN in discouraging the use of the syllables used in an established non-proprietary name since the use of these syllables may interfere with the development of new nonproprietary names.

The Committee finds the proposed name unacceptable for the reason stated above.

CDER Labeling and Nomenclature Committee

**ANESTHETIC AND LIFE SUPPORT DRUGS ADVISORY COMMITTEE**  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Pilot Drug Evaluation Staff  
January 17-18, 1995  
Parklawn Building, Conference Rms. D and E  
5600 Fishers Lane, Rockville, Maryland

January 17, 1995

Open Session

**NDA 20-478 SEVOFLURANE®-ABBOTT LABORATORIES**

8:30 a.m. Call to Order - James Eisenach, M.D., Chairman

Opening Remarks and Announcements (COI)  
Isaac F. Rouben, Ph.D., Executive Secretary  
Robert F. Bedford, M.D., Acting Director  
Pilot Drug Evaluation Staff

9:00 a.m. Open Public Hearing

**Sponsor Presentation**

**FDA Presentation**

**Clinical Trials Overviews by the Primary Reviewers**

Renee Landesman, M.D.: Metabolism and Safety

C. Philip Larson, M.D.: Adults, Outpatients, and  
inpatients

Robert Merin, M.D.: Cardiovascular Pharmacology/  
Cardiac Surgery

Margaret Wood, M.D.: Pediatric Anesthesia

Marie Young, M.D.: Elderly, Hepatic and Renal  
Failure

Robert Bedford, M.D.: Neurosurgical Anesthesia

James Eisenach, M.D.: OB Anesthesia/Muscle  
Relaxant Interaction

Daniel Spyker, M.D.: Clinical Safety Review  
Barbara Palmisano, M.D.

**Open Committee Discussion**

Questions from the Advisory Committee Members  
to sponsor and/or FDA clinical reviewers:

Pharmacology - Anwar Goheer, Ph.D./Almon Coulter, Ph.D.  
Pharmacokinetics - Peter Lockwood, M.S.  
Biostatistics - Hoi Leung, Ph.D.

11:00 a.m.      Closed Session

12 noon          Lunch

1:00 p.m.      Review of the Product Labeling  
(Prescribing Information)

5:00 p.m.      End of day one

**ANESTHETIC AND LIFE SUPPORT DRUGS ADVISORY COMMITTEE**

Food and Drug Administration  
Center for Drug Evaluation and Research  
Pilot Drug Evaluation Staff

January 17-18, 1995  
Parklawn Building, Conference Rms. D and E  
5600 Fishers Lane, Rockville, Maryland

January 18, 1995

Open Session

8:30 a.m.           **Questions to the Committee**

**A. Phase IV -- Issues Identified by Primary Reviewers**

**1. Metabolism and Safety:**

- a. Are additional studies examining the production of Compound A from baralyme and sodalime needed?
- b. Should additional studies with Cytochrome P-450 2E1-inducers (isoniazid, EtOH) be performed?

**2. Obstetrical Anesthesia:**

Are additional studies on use of sevoflurane for cesarian section needed? If so, what studies are recommended?

**3. Neurosurgical Anesthesia:**

Are additional Studies on patients at risk for elevated intracranial pressure needed?

**4. Coronary Artery Disease:**

Are additional studies indicated for patients with significant coronary artery disease?

**5. Pediatric Patients:**

Is there increased post-operative agitation following sevoflurane? Should this be studied further?

**ANESTHETIC AND LIFE SUPPORT DRUGS ADVISORY COMMITTEE**

January 17-18, 1995

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Jerry G. Reves, M.D.  
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(page 1 of 2)

DECEMBER 5, 1994

Anesthetic and Life Support Drugs  
Advisory Committee

(page 2 of 2)

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Department of Anesthesia  
University of Pennsylvania  
3400 Spruce Street  
Philadelphia, Pennsylvania 19104-4283

# END

A handwritten signature or set of initials in black ink, consisting of several loops and curves, positioned above a horizontal line.

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J.H.M. RESEARCH & DEVELOPMENT, INC. 5776 SECOND STREET, N.E. WASH. DC 20011