CORRESPONDENCE

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Is There Equivalence between Compound A and a Synthetic Olefin?

To the Editor:—I read with interest the editorial[1] and the two articles on the toxicity of compound A in rats by Gonsowski et al.[2,3]

The running head on each page of these articles is "Injury from a Sevoflurane Breakdown Product", which I believe is misleading because the studies were conducted with a synthetic olefin, not compound A generated as a result of the interaction between sevoflurane and carbon dioxide absorbents. No studies have been conducted to evaluate the equivalence between the synthetic olefin and compound A generated "naturally" in a clinical situation. As noted in the articles, the primary contaminant of the synthetic product is tetrahydrofurane, which itself has toxic properties. Naturally occurring compound A does not contain tetrahydrofurane. Moreover, the olefin was synthesized for these studies by Anaquest.[2]

Sevoflurane has been administered to more than 1.5 million patients in Japan with no reports of toxicity associated with either compound A or fluoride ions. In addition, more than 3,000 patients in the clinical development program being conducted by Abbott Laboratories have received sevoflurane. The flow rate in at least 400 of these cases was 2–4 l/min.* Because sevoflurane interacts with carbon dioxide absorbents to produce compound A, it can be assumed that these patients were exposed to some level of compound A. No clinical signs or symptoms of toxicity were reported in these cases.

The safety profile of sevoflurane compares very favorably with other inhalation agents (isoflurane, enflurane, halothane) in our clinical trials. The incidence of adverse events is similar for all agents. Although the conclusions of the authors of these laboratory studies are interesting, it is unlikely that they have any clinical relevance.

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3. Gonsowski CT, Laster MJ, Eger EI II, Ferrell LD, Kerschmann RL: Toxicity of compound A in rats: Effect of increasing duration of administration. ANESTHESIOLOGY 80:566–575, 1994

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* Abbott Laboratories. Data on file.

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In Reply:—Callan wonders whether the synthetic compound A used in our experiments is equivalent to compound A resulting from the degradation of sevoflurane. She reasons that a contaminant, tetrahydrofurane, in our synthetic compound A may have exerted an independent injurious effect. This issue was discarded in the peer review of our articles[1,2] because the concentration of tetrahydrofurane that produces injury greatly exceeds the highest concentration we applied. As determined by our gas chromatographic analysis and the analysis provided by Anaquest, the compound A we used included, at most, 1% tetrahydrofurane. If all of the tetrahydrofurane vaporized to produce 1% of 400 ppm (the highest concentration of compound A we applied), the total would be 4 ppm. Because the lethal concentration (LC_{50}) of tetrahydrofurane for a 3-h exposure in rats is 21,000 ppm,[3] the LC_{50} we found for compound A of 331 ppm might have included a concentration of tetrahydrofurane that was 1/5,000th the lethal level. The nearly identical finding by Morio et al.,[4] who used compound A obtained from Maruishi, Abbott's commercial partner, corroborates our result for compound A.

Callan believes that clinical evidence supports the safety of sevoflurane. The observation that "sevoflurane has been administered to more than 1.5 million patients in Japan with no reports of toxicity associated with either compound A or fluoride ions" seems to overlook three reports of severe hepatic injury associated with administration of sevoflurane.[5–7] However, the issue is not the toxicity of sevoflurane but that associated with its degradation product, compound A. The perceived low toxicity of sevoflurane must be considered in the context of the methods of its administration. In Japan, most inhaled anesthetics are given in high inflow rates that minimize

rebreathing and thereby minimize the concentrations of compound A breathed by the patient. High flow rates also limit increases in temperature in the absorbent and therefore limit production of compound A. Similarly, the absence of toxicity in patients given sevoflurane in inflow rates of 2–4 l/min is not reassuring.

If our results in rats apply to humans (and they may not), then the injury that might result from administration of sevoflurane would be subtle because, in most patients, the compound A concentrations produced in closed circuits or low-flow systems would damage only a small fraction of renal cells. Such injury would be difficult to ascertain with ordinary tests of renal function.

The several virtues of sevoflurane may promote its acceptance. Part of that acceptance will be based on the data described by Callan. Part of the acceptance also will depend on a complete description of the toxicity of sevoflurane and compound A. Because our data in rats may not apply to primates, we need data for primates on the *threshold* of injury from compound A. We also need to know the lethal concentration in primates. Finally, we must determine, for a large number of patients, the range of compound A concentrations attainable during low-flow anesthesia, plus the effect of different flow rates, patient sizes, lengths of anesthesia, and choices of carbon dioxide absorbent. Although subtle renal changes may not be clinically relevant, the clinician might want data sufficient to make his or her own judgment.

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Head Immobilization in Eye Surgery

To the Editor:—As an ophthalmologist, I am interested in preventing eye injuries during surgery. In a recent closed claims analysis, Gild *et al.*[1] identified patient movement during eye surgery as the second most common mechanism of ophthalmologic injury, accounting for 30% of the eye injury claims against anesthesiologists.

I would like to share with my anesthesia colleagues a simple method for preventing head movement during eye surgery.

The technique for head immobilization involves taping the patient's forehead to the operating table, in conjunction with a standard donut or trough-shaped pillow. Two-inch-wide cloth tape is used and should be wrapped twice around the patient's head and the table in one continuous piece (fig. 1). The tape is most effective when placed in a diagonal fashion; for surgery on the left eye, the tape is placed from the lower right to the upper left (fig. 2). The tape needs to be as close to the brow as possible without interfering with the sterile field; and it needs to be placed directly on the patient's skin. The contralateral eye must be checked after placement of the tape, because a lagophthalmos of this eye has occasionally been noted as a result

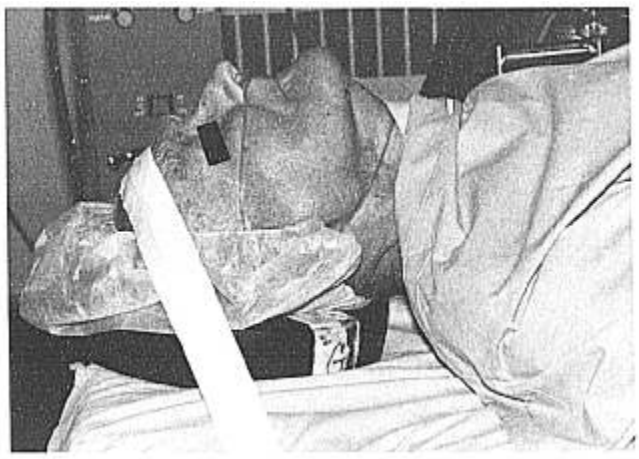

Fig. 1. Side view of head taping.