

CORRESPONDENCE

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Is There Equivalence between Compound A and a Synthetic Olefin?

To the Editor:—I read with interest the editorial¹ 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 tetrahydrofuran, which itself has toxic properties. Naturally occurring compound A does not contain tetrahydrofuran. 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.

* 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, tetrahydrofuran, 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 tetrahydrofuran 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% tetrahydrofuran. If all of the tetrahydrofuran 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 (LC₅₀) of tetrahydrofuran for a 3-h exposure in rats is 21,000 ppm,³ the LC₅₀ we found for compound A of 331 ppm might

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.

Clair M. Callan, M.D.
Divisional Vice President
HPD Medical and Regulatory Affairs and
Advanced Research
Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-380

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have included a concentration of tetrahydrofuran 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