Anesthesiology
50:272–273, 1979

To the Editor:—The report by Stacey, Priestly and Hall[1] suggests that methoxyflurane, chloroform, halothane, and enflurane have toxic effects on isolated rat hepatocytes. Further, they suggest that chloroform and methoxyflurane have comparable toxic effects, and that these toxic effects are considerably greater than those produced by halothane. The effects of halothane are said to be significantly greater than those of enflurane. I believe that the failure of these investigators to measure or estimate the anesthetic partial pressures they used and relate these to some index of potency compromises their thesis. I have calculated the partial pressures they used, and converted these to MAC multiples. The resulting data do not support the conclusions they made.

The volume of vapor produced by one microliter (μl) of agent (V) was calculated from values for specific gravity, molecular weight, and the gas laws (table 1). The partition coefficient for the 2-ml solution (λs) was estimated from published values for Krebs' solution[2] or saline solution[3] or serum or blood[3] (table 1). I assumed that the 2 ml was effectively 1.5 ml of Krebs' solution or saline solution and 0.5 ml of serum or blood. The concentration produced in the gas phase by 1 μl in the final system (2 ml of solution plus a 23 ml gas phase) was estimated as 100 V/μl (2 λs + 23). The concentrations produced by the 2.5-, 5-, 10-, 15- and 20-μl additions were calculated by multiplying the volume added by the percentage produced by 1 μl. Finally, these percentages were converted to MAC multiples by dividing by MAC.[4]

I then replotted the data from Stacey, Priestly and Hall for change in alanine aminotransferase (fig. 1). I chose the data for alanine aminotransferase release since such release is a sensitive indicator of hepatic injury. These data then were again replotted using MAC multiples instead of microliters of anesthetic injected (fig. 2).

Figure 2 and figure 1 lead to quite different conclusions. In figure 2 it is not possible to discriminate between the injurious effects of enflurane, halothane, and methoxyflurane. Chloroform does appear to be more toxic, but even with chloroform, no evidence of toxicity is seen at 5.7 times MAC. With the other three agents, concentrations exceeding 10 to 15 times MAC are needed. The highest enflurane MAC multiple tested was 7.9. Similar conclusions are obtained

Table 1. Data Used to Convert Microliters Injected to MAC Multiples.

	Vapor Made by 1 μl of Anesthetic at 37 C, 1 atm (ml)	Solution/Gas Partition Coefficient	Concentration Produced by 1 μl Added to 2 ml Solution + 23 ml Gas Space	MAC	Saturated Vapor Pressure at 37 C (Per Cent of 1 atm)
Methoxy-flurane	0.221	6.1	0.628	0.22	7.4
Chloroform	0.317	6.0	0.906	0.8	43.4
Halothane	0.241	1.14	0.953	0.95	63.2
Enflurane	0.209	1.03	0.834	2.1	45.4

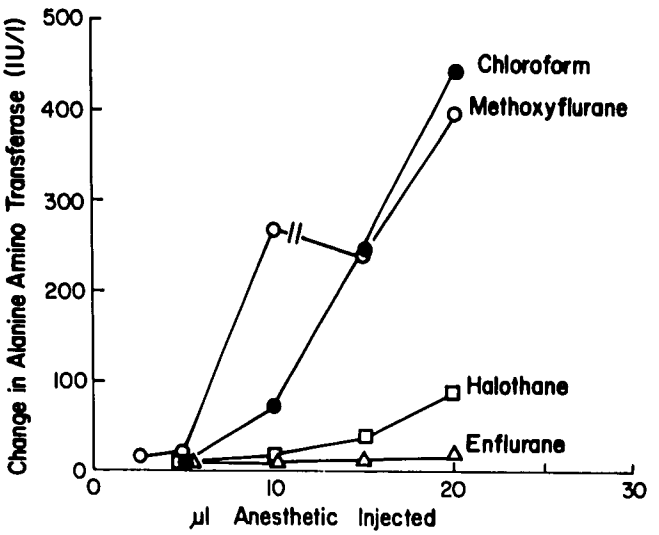

Fig. 1. This figure displays Stacey, Priestly and Halls' data for the effects of chloroform, methoxyflurane, halothane, and enflurane on the release of alanine aminotransferase from isolated rat hepatocytes. The coordinates are identical to those used in the original publication. The abscissa gives the microliters of liquid anesthetic added to 2 ml of cell suspension plus 23 ml of overlying gas space. The breaks in the methoxyflurane graph in this figure and figure 2 indicate the volume of methoxyflurane needed to produce a saturated solution.

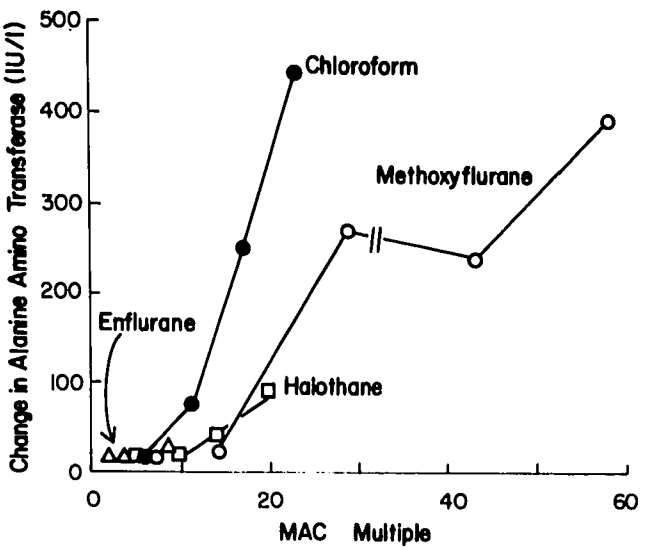

Fig. 2. The data from figure 1 are reproduced but the abscissa is altered by converting microliters of anesthetic to MAC multiples.

by replotting the other data from Stacey, Priestly and Hall's study.

The toxicity of very high anesthetic doses may be unrelated to biodegradation. The partial pressures of halothane or enflurane used far exceed those necessary to saturate the enzymes responsible for halothane or enflurane metabolism[5,6] and, hence, the amount of biodegradation probably does not vary over the ranges applied. On the other hand, the higher partial pressures used approach or equal (methoxyflurane) the saturated vapor pressures for these agents (table 1): for chloroform the highest (20 μl) dose is 42 per cent of the saturated vapor pressure; for halothane it is 30 per cent; for enflurane it is 37 per cent. Such high concentrations may injure by physical rather than metabolic effects. That the saturated vapor pressure for methoxyflurane is exceeded at the 15- and 20-μl doses may explain why these higher doses did not produce significantly more injury than the 10-μl dose.

I share the view of Stacey, Priestly and Hall that we need to understand better the conditions that affect the toxicity of halogenated volatile anesthetics. As they suggest, it would be desirable to be able to investigate those conditions through studies of *in-vitro* preparations, which can be well controlled and are far less expensive than *in-vivo* models. The above discussion emphasizes the importance of relating the doses of anesthetic used in such studies to some index of anesthetic potency.

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(Accepted for publication September 6, 1978.)

Anesthesiology
50:273–274, 1979

To the Editor:—Stacey *et al.*[1] have compared the *in-vitro* cytotoxicity of chloroform with those of halothane, enflurane, and methoxyflurane in freshly isolated rat liver cell suspensions. They conclude that the "relative order of cytotoxic potencies was found to be chloroform = methoxyflurane > halothane > enflurane" and that "extrapolation of our results to the clinical situation infers that enflurane has a lower potential for hepatoxicity than halothane." We differ with these interpretations and their rejection of the possibility that their results could be explained by the differing physicochemical properties of the volatile anesthetics.

We have replotted their data for changes of intracellular potassium ion content (their figure 1) using estimated tissue concentrations expressed as MAC

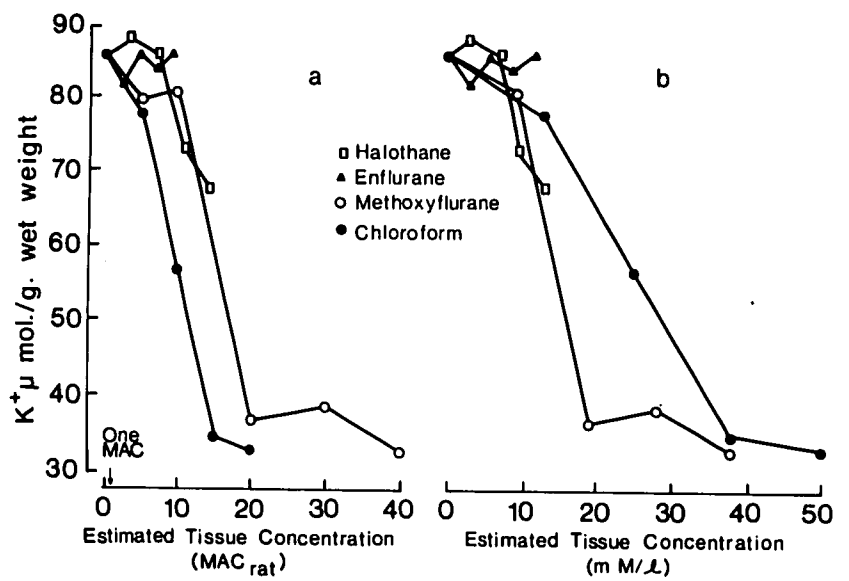

FIG. 1. Replotted data for changes of intracellular potassium ion content.