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Mazze R I, Trudell J R & Cousins M J. Methoxyflurane metabolism and renal dysfunction: clinical correlation in man. *Anesthesiology* 35:247-52, 1971.
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This was the first controlled study to demonstrate that postoperative nephrotoxicity in surgical patients anesthetized with methoxyflurane was due to biodegradation of the anesthetic to inorganic fluoride. Metabolic pathways were proposed to support the hypothesis, since confirmed, that inorganic fluoride caused methoxyflurane nephrotoxicity. [The SCF® indicates that this paper has been cited in over 190 publications since 1971.]

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"In 1966, Crandell^{1,2} reported that methoxyflurane caused high-output renal insufficiency in surgical patients. However, because of numerous errors in study design and lack of confirmatory studies, most anesthesiologists, myself included, did not accept Crandell's conclusion and methoxyflurane usage actually increased during the next five years to a rate of approximately two million administrations per year. To set aside what I believed was an unfair indictment, I designed a prospective, randomized, controlled clinical study³ which would overcome the flaws in Crandell's work. To my surprise, all 12 patients administered methoxyflurane showed signs of renal dysfunction. Just prior to publication of this study, Taves⁴ reported the case of a patient anesthetized with methoxyflurane who had an elevated plasma fluoride level and clinical nephrotoxicity. Michael Cousins, James Trudell, and I (the cited article) then measured inorganic fluoride and oxalic acid levels in the stored serum of patients from my earlier study.³ We showed a correlation between the degree of nephrotoxicity and the extent of methoxyflurane biotransformation to these metabolites and suggested that inorganic fluoride was the principal nephrotoxin. For the first time, a clear cause-and-effect relationship had been estab-

lished between methoxyflurane administration, its biotransformation to inorganic fluoride, and the clinical syndrome of postanesthetic high-output renal insufficiency.

"Subsequently, Cousins and I developed an animal model for methoxyflurane nephrotoxicity in Fischer 344 rats in which we could demonstrate dose-related biochemical and renal morphological lesions similar to those seen in humans.⁵ In my opinion, this is one of the best animal models of a clinical disease entity available to date. We followed this study with several other animal studies in which we demonstrated that: induction of hepatic microsomal enzymes increased the extent of the renal lesion; there was toxic interaction between nephrotoxic antibiotics, such as gentamicin, and methoxyflurane; and oxalic acid was not of primary importance in the methoxyflurane renal lesion. In later clinical studies, we were able to precisely establish the dose-related nature of the methoxyflurane renal lesion and to demonstrate that the threshold level of inorganic fluoride necessary to produce nephrotoxicity was approximately 40-50 μM .⁶ In addition to *in vivo* human and animal studies, we performed *in vitro* studies with hepatic microsomal preparations in which we compared the defluorination and nephrotoxic potential of methoxyflurane with that of the other clinically available fluorinated inhalation anesthetics—halothane, enflurane, and isoflurane—and with several experimental agents.

"Since 1971, my laboratory has published more than 50 scientific articles relating to the defluorination and renal effects of anesthetic agents. The cited article established the basis for these studies and those of other investigators studying anesthetic nephrotoxicity. As a result, methoxyflurane has all but dropped from clinical usage and most hospital pharmacies do not even have a bottle on their shelves. In the early 1970s, there was a great deal of interest in our studies and pressure from the manufacturers of methoxyflurane regarding our work, so there was a constant air of excitement in the laboratory. The atmosphere is less charged today, but we have a sense of satisfaction knowing that our research helped to shape clinical practice and, no doubt, to decrease anesthetic morbidity and mortality. The subject has recently been reviewed.⁷

1. Crandell W B, Pappas S G & Macdonald A. Nephrotoxicity associated with methoxyflurane anesthesia. *Anesthesiology* 27:591-607, 1966.
2. Crandell W B. Citation Classic. Commentary on *Anesthesiology* 27:591-607, 1966. *Current Contents/Life Sciences* 22(30):10, 23 July 1979.
3. Mazze R I, Shue G L & Jackson S H. Renal dysfunction associated with methoxyflurane anesthesia: a randomized, prospective clinical evaluation. *J. Amer. Med. Assn.* 216:278-88, 1971. (Cited 135 times.)
4. Taves D R, Fry B W, Freeman R B & Gilles A J. Toxicity following methoxyflurane anesthesia. II. Fluoride concentrations in nephrotoxicity. *J. Amer. Med. Assn.* 214:91-5, 1970. (Cited 160 times.)
5. Mazze R I, Cousins M J & Kosek J C. Dose-related methoxyflurane nephrotoxicity in rats: a biochemical and pathological correlation. *Anesthesiology* 36:571-87, 1972. (Cited 115 times.)
6. Cousins M J & Mazze R I. Methoxyflurane nephrotoxicity: a study of dose-response in man. *J. Amer. Med. Assn.* 225:1611-16, 1973. (Cited 120 times.)
7. Mazze R I. Nephrotoxicity of fluorinated anaesthetic agents. (Mazze R I, ed.) *Inhalation anaesthesia*. London: Saunders, 1983. p. 469-84.