J Anesth (1997) 11:32–37

Journal of
Anesthesia

Studies of the mechanism of nephrotoxicity of compound A in rats*

J.L. Martin[1], L. Kandel[2], M.J. Laster[2], R.L. Kerschmann[3], and E.I. Eger II[2]

[1] Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins Medical Institutions, Baltimore, MD 21287, USA
Departments of [2] Anesthesia and [3] Pathology, University of California, San Francisco, CA 94143, USA

Abstract: CO_2 absorbents acting on sevoflurane produce compound A [$CF_2 = C(CF_3)OCH_2F$]. Rats breathing 25–50 ppm of compound A for 3–12 h demonstrate corticomedullary renal injury. Several halogenated alkenes also produce a well described corticomedullary lesion by conversion of glutathione conjugates of these alkenes to cysteine s-conjugates and subsequent metabolism by renal cysteine conjugate β-lyase to nephrotoxic halothionoacetyl halides. We tested whether a similar mechanism explained the nephrotoxicity of compound A or whether an oxidative metabolism of compound A by cytochrome P-450 was required for the induction of nephrotoxicity. A closed rebreathing system was used and male Wistar rats were exposed for 1 h to: (1) oxygen alone; (2) 800 ppm compound A; (3) 800 ppm compound A after pretreatment with intraperitoneal aminooxyacetic acid (AOAA), 0.5 mmoles/kg, an inhibitor of renal cysteine conjugate β-lyase; (4) 600 ppm compound A; (5) 600 ppm compound A after pretreatment with intraperitoneal AOAA, 0.50 mmoles/kg plus acivicin (AT-125), 0.25 mmoles/kg, an inhibitor of gamma glutamyl transpeptidase; (6) 600 ppm compound A after pretreatment with 1600 mg/kg piperonyl butoxide (PB) subcutaneously, and (7) 600 ppm compound A after pretreatment with 100 mg/kg 1-aminobenzotriazole (ABT) by intraperitoneal injection (both PB and ABT inhibit cytochrome P-450s). All rats were killed 24 h following exposure to compound A or oxygen, or to pretreatments without compound A, and the kidneys were collected for histological analysis. Pretreatments given without compound A did not cause renal injury. Necrosis was found in 20.9 ± 16.7% (mean ± SD) of corticomedullary tubule cells following exposure of Wistar rats to 600 ppm compound A. Pretreatment with AOAA plus AT-125 increased necrosis to 57.9 ± 32.6%, ($P < 0.005$). PB or ABT given prior to compound A increased corticomedullary injury to 39.0 ± 31.4% ($P < 0.02$) and 51.2 ± 31.8% ($P < 0.025$), respectively. In rats exposed to 800 ppm compound A, pretreatment with AOAA increased necrosis from 63.8 ± 30.1% to 81.2 ± 27.7% ($P < 0.1$). Unlike many other halogenated alkenes, compound A does not appear to produce renal injury by conversion of a cysteine S-conjugate to a toxic thiol, nor does injury require metabolism mediated by cytochrome P-450. Injury may result from direct toxicity of compound A or by an undetermined metabolic pathway.

Key words: Anesthetics, Volatile, Sevoflurane, Toxicity, Compound A

Address correspondence to: J.L. Martin

Received for publication on June 22, 1995; accepted on October 9, 1996

*This article is accompanied by an editorial. Please see p.1–2.

Introduction

Soda lime and Baralyme (Chemtron/Allied Inc., St. Louis, MO, USA) brand absorbent dehydrofluorinate sevoflurane to form fluoromethyl-2,2-difluoro (trifluoromethyl) vinyl ether [$CF_2 = C(CF_3)OCH_2F$], also called compound A, which is nephrotoxic in rats [1,2]. The corticomedullary junction is the primary locus of injury (necrosis) in rates, and injury is both concentration- and time-dependent. The threshold for injury in rats is 25–50 ppm for 3- to 12-h exposures [2–4]. Similar exposures to compound A can occur in clinical practice when low-flow anesthesia is employed with sevoflurane, especially when higher concentrations of sevoflurane are applied [5,6]. Thus, concern regarding a potential for compound A nephrotoxicity in humans.

Halogenated alkenes structurally similar to compound A (in that all are halogenated and have unsaturated bonds), such as tetrafluorethene ($CF_2 = CF_2$) and chlorotrifluoroethane ($CCIF = CF_2$), produce corticomedullary junction necrosis [7–9] by an extensively studied mechanism [10–12]. An initial reaction of the alkene with glutathione (GSH), catalyzed by hepatic GSH S-transferase, forms a GSH S-conjugate. The GSH conjugate is metabolized to the corresponding cysteine S-conjugate by γ-glutamyl transpeptidase (γ-GT), to form a cysteinylglycine conjugate, which is then converted into cysteinyl-GSH by cysteinylglycine dipeptidase. Next, translocation of the cysteine conju-

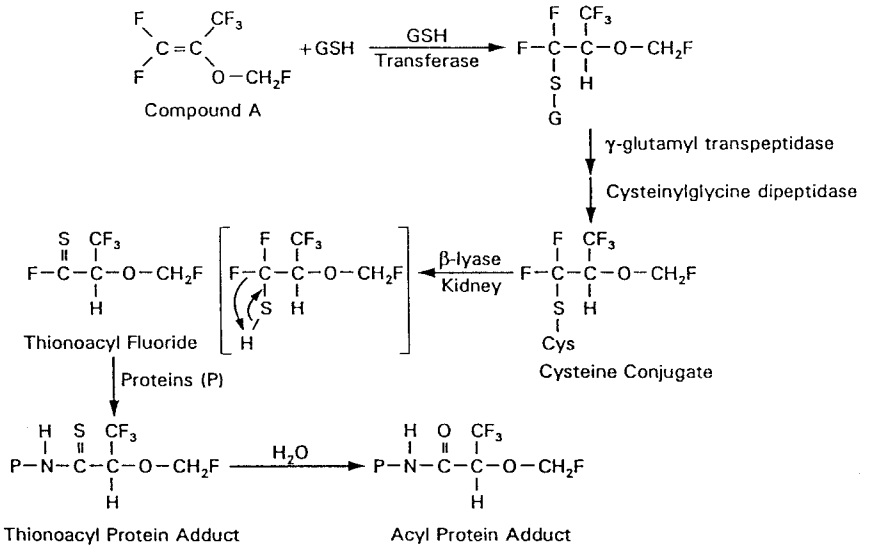

Fig. 1. Proposed pathway for the metabolic activation of compound A shows formation of an intrahepatic glutathione (*GSH*) conjugate of compound A that is translocated to the kidney, where γ-glutamyl transpeptidase, cysteinylglycine dipeptidase, and renal cysteine conjugate β-lyase catalyze the formation of a nephrotoxic thiol

gate to the kidney occurs, with conversion there by renal cysteine conjugate β-lyase to an unstable thiol that can acylate kidney proteins. Alternatively, the glutathione S-conjugate may be translocated to the kidney, followed by conversion to the cysteine S-conjugate and the toxic thiol. Figure 1 presents an analogous pathway of metabolic activation of compound A.

In the present study we tested, by applying inhibitors of γ-GT and renal cysteine conjugate β-lyase, whether a cysteine conjugate of compound A mediates compound A toxicity. These agents block or markedly attenuate the nephrotoxicity of several halogenated alkenes [13–15].

Materials and methods

Test compounds and exposure of rats to compound A

Compound A was supplied by Ohmeda (Liberty Cornen, NJ, USA) [3] and was >99% pure by gas chromatography analysis. Aminooxyacetic acid (AOAA), piperonyl butoxide, and 1-aminobenzotriazole (ABT) were obtained from Aldrich Chemical (Milwaukee, WI, USA). Acivicin, L-(α S,5S)-α-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid) (AT-125), was obtained from Sigma Chemical (St. Louis, Mo., USA).

With the approval of the Animal Research Committee, we tested the nephrotoxicity of compound A in 140 (data for 134 surviving animals) male specific-pathogen-free, 5- to 6-week-old Wistar rats, ranging in weight from 146 to 180 g. As described in detail elsewhere [3], rats were exposed to oxygen with or without compound A in a closed rebreathing system for 1 h as follows: (1) 30 rats breathed oxygen only; (2) 20 rats breathed 800 ppm compound A (positive control); (3) 10 rats breathed 800 ppm compound A after pretreatment by intraperitoneal injection of 0.50 mmoles/kg AOAA; (4) 15 rats breathed 600 ppm compound A (positive control); (5) 15 rats breathed 600 ppm compound A after pretreatment by intraperitoneal injection of 0.50 mmoles/kg AOAA plus 0.25 mmoles/kg AT-125 (compounds that block conversion of glutathione conjugates to cysteine conjugates). For studies 2–5, each exposure involved 5 positive control rats and 5 rats given AOAA plus AT-125 (concurrent administration of compound A); (6) 10 rats breathed oxygen only after pretreatment with 0.50 mmoles/kg AOAA plus 0.25 mmoles/kg AT-125 (drug control); (7) 10 rats breathed oxygen alone following i.p. administration of 0.5 mmoles/kg AOAA; (8) 10 rats received 1600 mg/kg piperonyl butoxide subcutaneously, 45 min before breathing 600 ppm compound A; (9) 10 rats received 100 mg/kg 1-aminobenzotriazole (ABT) intraperitoneally, 2 h before breathing 600 ppm compound A; (10) 5 rats received 1600 mg/kg piperonyl butoxide subcutaneously, 45 min before breathing oxygen; and (11) 5 rats received 100 mg/kg ABT intraperitoneally, 2 h before breathing oxygen. Table 1 lists the above schedules.

All rats were killed after 24 h by immersion in carbon dioxide. The kidneys were removed within 5 min after cessation of breathing, and specimens were immediately placed in 10% buffered formalin. Paraffin sections were made, stained with hematoxylin and eosin, randomly ordered in a fashion blinded to the treatment accorded each rat, and histologically scored (by R.L.K.) for injury by determining whether renal injury had occurred and the percentage of the tubule cells in the corticomedullary junction that were damaged. Thirty to forty high-power fields (magnification 20 ×) were examined to ascertain whether damage was present and

Table 1. Exposure schedules

Pretreatment	Number of rats for which data were obtained		
	Oxygen only	800 ppm compound A	600 ppm compound A
Saline	30	20	15
AOAA only	10	8[b]	—
AOAA + AT-125	7[a]	—	14[c]
Piperonyl butoxide	5	—	10
1-Aminobenzotriazole	5	—	10

AOAA, Aminooxyacetic acid; AT-125, acivicin.
[a] Three rats died.
[b] Two rats died.
[c] One rat died.

the type of damage. Three to four low-power fields (magnification 4 ×) per cross-section area of the kidney were used to estimate the portion of parenchyma that was necrotic or pre-necrotic (shrunken nuclei and condensation of cytoplasm) in each of three layers (cortex, corticomedullary junction, and medulla) and overall. Three to four low-power fields covered the entire kidney section.

Statistical methods

We used unpaired *t*-tests, χ^2 analysis, or Fisher exact probability tests for comparisons. We accepted $P < 0.05$ as indicating statistical significance.

Results

Breathing 600 ppm or 800 ppm compound A did not cause anesthesia in any rat and all rats moved at intervals during the exposure periods. Exposure appeared to be irritating. Rats squinted or kept their eyes closed. No rat showed evidence of gross neurologic abnormalities. Two rats given AOAA died during exposure to 800 ppm compound A. Three rats given the combination of AOAA plus AT-125 followed by oxygen died during or after exposure, and one rat given AOAA plus AT-125 died during exposure to 600 ppm compound A.

Rats exposed to 800 or 600 ppm of compound A had necrosis of corticomedullary junction tubules. The necrosis was greater with 800 ppm compound A exposure (63.8% necrotic), as compared to 600 ppm exposure (20.9% necrotic). Pretreatment with AOAA alone increased nephrotoxicity after 800 ppm compound A (81.2% necrotic). Pretreatment with AOAA plus AT-125 increased necrosis after exposure to 600 ppm compound A (57.9% necrotic) (Table 2). For all pretreatments, rats exposed to oxygen alone showed no evidence of nephrotoxicity. To test whether cytochrome P-450 mediated the nephrotoxicity caused by compound A, inhibitors of cytochrome P-450 were studied. Pretreatment with either PB or ABT significantly increased compound A nephrotoxicity, from 21% to 39% and 51%, respectively (Table 2). Rats exposed to oxygen alone after pretreatment with either PB or ABT showed no evidence of nephrotoxicity.

Table 2. Corticomedullary junction injury associated with different treatments

Pretreatment	Percent corticomedullary junction necrosis		
	Oxygen only	800 ppm compound A	600 ppm compound A
Saline	0 ± 0	63.8 ± 30.1	20.9 ± 16.7
AOAA only	0 ± 0	81.2 ± 27.7	ND[a]
AOAA + AT-125	0 ± 0	ND	57.9 ± 32.6*
Piperonyl butoxide	0 ± 0	ND	39.0 ± 31.4**
1-Aminobenzotriazole	0 ± 0	ND	51.2 ± 31.8***

Values are means ± SD. Compared to the control (saline-treated) value at 600 ppm, the values for treated rats increased or tended to increase (* $P < 0.005$; ** $P < 0.02$; *** $P < 0.025$, respectively). The dose of AOAA was 0.5 mmoles/kg, intraperitoneally. The dose of AT-125 was 0.25 mmoles/kg, intraperitoneally. The dose of piperonyl butoxide was 1600 mg/kg subcutaneously, and the dose of ABT was 100 mg/kg, intraperitoneally, as described in the Methods section.
[a] ND, Not determined.

Discussion

Compound A is structurally related (by halogenation and unsaturation) to tetrafluoroethene (TFE), chlorotrifluoroethene (CTFE), and hexafluoropropylene (HFP) [9], all nephrotoxic haloalkenes of moderate toxicity that form GSH conjugates which undergo metabolic activation to toxic thiol metabolites [16,17]. A GSH conjugate of compound A would be expected to be degraded to a cysteine S-conjugate in vivo, by the stepwise cleavage of the γ-glutamyl and glycine residues, reactions catalyzed by γ-glutamyltransferase (γ-GT) and cysteinylglycine dipeptidase, respectively. The mercapturic acid of compound A could be formed from the cysteine S-conjugate, or alternatively, the cysteine S-conjugate could be converted in the kidney by renal cysteine conjugate β-lyase into the reactive metabolite, 3,3,3-trifluoro-2-fluoromethoxy-thionoproprionyl fluoride, $CF_3CH(OCH_2F)CSF$ (Fig. 1). This reactive metabolite would be expected to acylate tissue proteins, leading to toxicity. In addition to TFE, CTFE, and HFP, hexachloro-1,3-butadiene (HCBD) [18] also produces marked nephrotoxicity and forms a cysteine conjugate that is a substrate for renal cysteine conjugate β-lyase [12]. S-(2-bromo-2-chloro-1,1-difluoroethyl)-*N*-acetyl-L-cysteine (BCDFC) has been identified in the urine of humans following halothane exposure [19], and arises from the halothane degradation product, 2-bromo-2-chloro-1,1-difluoroethane (BCDFE). BCDFC may also serve as a substrate for renal cysteine conjugate β-lyase, leading to the formation of the toxic thiol, bromochlorothioacetyl fluoride. Indeed, the glutathione conjugate (BCDFG) and the cysteine conjugate (BCDFC) of BCDFE were shown to be nephrotoxic in vivo in the rat [20].

Gamma glutamyltransferase and cysteinylglycine dipeptidase are brush border enzymes that are present in high concentrations in the renal tubule. Rodents have much higher renal γ-GT and dipeptidase activities than humans [21], and total cysteine conjugate β-lyase activity in human kidney cytosol is 10% of that in rat kidney cytosol [22]. Thus, if the above mechanism explains the injury seen in rats, humans may be less vulnerable to the toxic effects of compound A.

Blocking the conversion of cysteine S-conjugates of several haloalkenes to toxic thiols decreases or prevents renal proximal tubular cell injury [13–15]. We used doses of AOAA (an inhibitor of pyridoxal phosphate-dependent enzymes) that cause an 85%–90% in-vivo inhibition of cysteine conjugate β-lyase enzymes [13–15]. Similarly, significant inhibition of nephrotoxicity followed the administration of AT-125 (an irreversible inhibitor of γ-GT) [23,24]; 800 ppm compound A in untreated rats produced nearly 64% corticomedullary necrosis (Table 2). This dose of compound A was initially chosen because we expected to find a marked decrease in nephrotoxicity as a result of pretreatments with the inhibitors, AOAA and AT-125, (i.e., a greater injury in positive control rats would provide a more sensitive test of protection). However, with AOAA pretreatment the necrosis was increased to 81.2%, and two of ten animals died. Because of this unexpectedly increased toxicity, 600 ppm of compound A was used for all subsequent studies. This lower concentration produced 21% corticomedullary necrosis in untreated rats (Table 2). Pretreatment with AOAA plus AT-125 increased renal corticomedullary necrosis following exposure to 600 ppm of compound A to nearly 58% (Table 2). Thus, our results indicate that, for both 600 and 800 ppm, the renal cysteine conjugate β-lyase enzymes act to detoxify compound A, and inhibition of this pathway shunts reactive intermediates to more toxic avenues. This suggests that either a cysteine conjugate, a glutathione conjugate, or compound A itself may be nephrotoxic. Other investigators have reported an increase in the toxic effects of glutathione-conjugated chlorohydroquinones [DC-(GSyl)HQ] and [TC-(GSyl)HQ] after treatment of rats in vivo with AT-125 [25]. AT-125 also fails to protect against either chloroethyl-GSH (CEG) [26]- or HCBD [27]-induced nephrotoxicity, suggesting a detoxifying role for γ-GT.

Two rats given AOAA died during exposure to 800 ppm compound A, while three rats given the combination of AOAA plus AT-125 followed by oxygen died during or after exposure; one rat given AOAA plus AT-125 died during exposure to 600 ppm compound A. For all pretreatments, rats exposed to oxygen alone showed no evidence of nephrotoxicity. Most likely, the deaths of these rats occurred because we were just below the median lethal dose (LD_{50}) for AOAA and AT-125.

Another potential mechanism that could explain the nephrotoxicity of compound A may occur through a cytochrome P-450-dependent metabolic pathway. Metabolism catalyzed by cytochrome P-450 would generate a reactive intermediate of similar structure to that formed via the renal cysteine conjugate β-lyase pathway described earlier. To ascertain the role of oxidative metabolism by cytochromes P-450 in the toxicity of compound A, the effects of the P-450 inhibitors piperonyl butoxide and 1-aminobenzotriazole (ABT) were studied. Piperonyl butoxide inhibits cytochromes P-450 after in-vivo administration [28], and the dose of ABT used in our study (100 mg/kg) selectively destroys 80% of both hepatic and renal cytochrome P-450 [29,30]. ABT at this dose does not affect phase II-dependent enzyme activities (such as glutathione conjugation) and produces no changes in hepatic or renal glutathione content [28]. Pretreatment with piperonyl butoxide increased corticomedullary necrosis to 39% (Table 2).

The lesion increased even more (51% necrotic) following pretreatment with ABT (Table 2). Since inhibition of cytochromes P-450 enhanced nephrotoxicity, these results indicate that cytochromes P-450 may catabolize compound A to less toxic intermediates.

In earlier rat studies of haloalkene renal toxicity, functional impairment of renal concentrating ability was expressed as a decline in urine solute concentration and increased water intake with increasing haloalkene concentrations [17]. For CTFE, functional impairment occurred at 100 ppm, approximately one-tenth the 4-h, median lethal concentration (LC_{50}) of 1000 ppm [31]. For HFP, the 4-h LC_{50} was 3000 ppm and the threshold for renal impairment was approximately 400 ppm [31]. For TFE, the values were 40000 ppm and 500 ppm, respectively [31]. Studies with compound A show that the threshold for histological necrosis is 25–50 ppm [3], approximately one-tenth the 4-h LC_{50} of 400 ppm [2], and this raises the concern that heretofore unidentified functional renal impairment may exist after compound A exposure in the rat.

The toxicity of compound A is of concern in the delivery of sevoflurane when low fresh gas flows are given, since higher inspired concentrations of compound A result under these conditions [5]. Concentrations of compound A seen in clinical practice (as high as 61 ppm) [5] approach the threshold for renal injury in the rat (25–50 ppm) [3]. However, such injury in patients might not be readily apparent, since functional impairment would not likely develop, and routine measures of renal function are poor predictors of nephrotoxicity [32]. Results from patients given high fresh gas flows (as occurs in Japan) may not adequately address concerns regarding the direct nephrotoxicity of compound A [33,34].

A recent report describes the identification in bile of GSH conjugates of compound A, as well as compound A-mercapturic acid conjugates, in the urine of male Sprague-Dawley rats following i.p. administration of compound A (1 mmole/kg) [35]. The investigators further reported that pretreatment with AOAA partially protected against compound A-induced diuresis and proteinuria, but failed to protect against glucosuria in male Fischer rats treated i.p. with compound A (0.2 mmoles/kg). No histology was reported in this study.

The results of our studies provide direct evidence that the mechanism that explains the nephrotoxicity of several haloalkenes does not explain the nephrotoxicity produced by compound A. Blockade of the renal cysteine conjugate β-lyase pathway that leads to production of a reactive thiol from such alkenes, and blockade of oxidative metabolism mediated by cytochrome P-450 significantly increase, rather than decrease, compound A nephrotoxicity. The fact that humans have much lower levels of β-lyase enzymes is of little consequence, since this pathway does not appear to be a major route of metabolism of compound A. The mechanism by which compound A produces nephrotoxicity remains unknown. Compound A itself may react directly with tissue macromolecules, leading to cellular injury; or, alternatively, compound A may mediate nephrotoxicity through the formation of toxic glutathione or cysteine conjugates, or through some as yet unknown pathway.

Acknowledgments. Supported by grants from Ohmeda Pharmaceutical Products Division (E.I.E., J.L.M.), The Anesthesia Research Foundation (E.I.E.), and The Robert Wood Johnson Foundation (J.L.M.). Dr. Eger is a paid consultant to Ohmeda Pharmaceutical Products Division.

References

1. Strum DP, Johnson BH, Eger EI II (1987) Stability of sevoflurane in soda lime. Anesthesiology 67:779–781
2. Morio M, Fuji K, Satoh N, Imai M, Kawakami U, Mizuno T, Kawai Y, Ogasawara Y, Tamura T, Negishi A, Kumagai Y, Kawai T (1992) Reaction of sevoflurane and its degradation products with soda lime. Anesthesiology 77:1155–1164
3. Gonsowski C, Laster M, Eger EI II, Ferrell L, Kerschmann R (1994) Toxicity of compound A in rats. Effect of a 3-hour administration. Anesthesiology 80:556–565
4. Gonsowski C, Laster M, Eger EI II, Ferrell L, Kerschmann R (1994) Toxicity of compound A in rats. Effect of increasing duration of administration. Anesthesiology 80:566–573
5. Frink EJ Jr, Mallan T, Morgan S, Brown E, Malcomson M, Brown BB Jr (1992) Quantitation of the degradation products of sevoflurane in two carbon dioxide absorbents during low-flow anesthesia in surgical patients. Anesthesiology 77:1064–1069
6. Bito H, Ikeda K (1994) Long-duration, low-flow sevoflurane anesthesia using two carbon dioxide absorbents. Quantitation of degradation products in the circuit. Anesthesiology 81:340–345
7. Potter CL, Gandolfi AJ, Nagle R, Clayton JW (1981) Effects of inhaled chlorotrifluoroethylene and hexafluoropropene on the rat kidney. Toxicol Appl Pharmacol 59:431–440
8. Odum J, Green T (1984) The metabolism and nephrotoxicity of tetrafluoroethylene in the rat. Toxicol Appl Pharmacol 76:306–318
9. Greene T, Odum J (1985) Structure/activity studies of the nephrotoxic and mutagenic action of cysteine conjugates of chloro- and fluoroalkenes. Chem Biol Interactions 54:15–31
10. Dekat W, Vamvaks S, Anders M (1989) Bioactivation of nephrotoxic haloalkenes by glutathione conjugation: Formation of toxic and mutagenic intermediates by cysteine conjugate β-lyase. Drug Metab Rev 20:43–83
11. Monks T, Anders M, Dekant W, Stevens J, Lau S, Van BP, J (1990) Glutathione conjugate mediated toxicities. Toxicol Appl Pharmacol 106:1–19
12. Dekant W, Anders M, Monks T (1993) Bioactivation of halogenated xenobiotics by S-conjugate formation. In: Anders MW (eds) Renal disposition and nephrotoxicity of xenobiotics. Academic, New York, pp 187–215
13. Elfarra AA, Anders MW (1984) Renal processing of glutathione conjugates. Role in nephrotoxicity. Biochem Pharmacol 33:3729–3732
14. Elferra AA, Jakobson IJ, Anders MW (1986) Mechanism of S-(1,2-dichlorovinylcysteinyl) glutathione-induced nephrotoxicity. Biochem Pharmacol 35:283–288

15. Anders MW, Lash L, Elferra AA (1986) Nephrotoxic amino acid and glutathione S-conjugates: Formation and renal activation. Adv Exp Med Biol 197:443–455
16. Hayden PJ, Ichimura T, McCann DJ, Pohl LR, Stevens JL (1991) Detection of cysteine conjugate metabolite adduct formation with specific mitochondrial proteins using antibodies raised against halothane metabolite adducts. J Biol Chem 266:18415–18418
17. Clayton JW (1977) Toxicology of fluoroalkenes: Review and research needs. Environ Health Perspect 21:255–267
18. Berndt WO, Mehendale HM (1979) Effects of hexachlorobutadiene (HCBD) on renal function and renal organic ion transport in the rat. Toxicology 14:55–65
19. Cohen EN, Trudell JR, Edmunds HN, Watson E (1975) Urinary metabolites of halothane in man. Anesthesiology 43:392–401
20. Finkelstein MB, Baggs RB, Anders MW (1992) Nephrotoxicity of the glutathione and cysteine conjugates of 2-bromo,-2-chloro-1,1-difluoroethane. J Pharmacol Exp Ther 261:148–1252
21. Hinchman C, Ballatori N (1994) Glutathione conjugation and conversion to mercapturic acids can occur as an intrahepatic process. J Toxicol Environ Health 41:387–409
22. Lash L, Nelson R, Van Dyke RA, Anders MW (1990) Purification and characterization of human kidney cytosolic conjugate β-lyase activity. Drug Metab Disp 18:50–54
23. Allen L, Meek R, Aeons A (1980) The inhibition of γ-glutamyl transpeptidase from human pancreatic carcinoma cells by L-(α S,5S)-α-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid (AT-125;NSC-163501). Res Commun Chem Pathol Pharmacol 27: 175–182
24. Reed DJ, Ellis WW, Meek RA (1980) The inhibition of γ-glutamyl transpeptidase and glutathione metabolism of isolated rat kidney cells by L-(α S,5S)-α-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid (AT-125;NSC-163501). Biochem Biophys Res Commun 94:1273–1277
25. Mertens JJWM, Temmink JHM, van Bladeren PJ, Jones TW, Lo HH, Lau SS, Monks TJ (1991) Inhihbition of γ-glutamyl transpeptidase potentiates the nephrotoxicity of glutathione-conjugated chlorohydroquinone. Toxicol Appl Pharmacol 110:45–60
26. Kramer RA, Greene KE, Fouremn GL, Reed DJ (1986) Nephrotoxicity of S-(2-chloroethyl)-GSH and S-(2-bromohydroquinone)-GSH. Evidence for multiple GSH conjugate transport systems in the kidney. Toxicologist 6:149
27. Davis ME (1984) AT-125 (Acivicin) does not prevent hexachlorobutadiene (HCBD) nephrotoxicity. Toxicologist 4:42
28. Lau SS, Monks TJ, Greene KE, Gillette JR (1984) The role of ortho-bromophenol in the nephrotoxicity of bromobenzene in rats. Toxicol Appl Pharmacol 72:539–549
29. Ortiz De Montellano PR, Matthews JM (1981) Autocatalytic alkylation of the cytochrome P-450 prosthetic haem group by 1-aminobenzotriazole. Biochem J 195:761–764
30. Mugford CA, Mortillo M, Mico BE, Tarloff JA (1992) 1-Aminobenzotriazole-induced destruction of hepatic and renal cytochromes P-450 in male Sprague-Dawley rats. Fundam Appl Toxicol 19:43–49
31. Clayton JW (1967) Fluorocarbon toxicity and biologic action. Fluorine Chemistry Rev 1:197–252
32. Kluwe WM (1981) Renal function tests as indicators of kidney injury in subacute toxicity studies. Toxicol Appl Pharmacol 57:414–424
33. Kobayashi Y, Ochiai R, Takeda J, Sekiguchi H, Fukushima K (1992) Serum and urinary inorganic fluoride levels after prolonged inhalation of sevoflurane in man. Anesth Analg 74:753–757
34. Higuchi H, Satoh T, Arimura S, Kanno M, Endoh R (1993) Serum inorganic fluoride levels in mildly obese patients during and after sevoflurane anesthesia. Anesth Analg 77:1018–1021
35. Jin L, Bailic TA, Davis MR, Kharasch ED (1995) Nephrotoxicity of sevoflurane compound A [(fluoromethyl-2,2-difluoro-1-(trifluoromethyl) vinyl ether] in rats: Evidence for glutathione and cysteine conjugate formation and the role of renal cysteine conjugate β-lyase. Biochem Biophys Res Commun 210:498–506