

Toxic Nephropathy: Environmental Chemicals

By Terry R. Van Vleet and Rick G. Schnellmann

The kidney is the target of numerous xenobiotic toxicants, including environmental chemicals. Anatomical, physiological, and biochemical features of the kidney make it particularly sensitive to many environmental compounds. Factors contributing to the sensitivity of the kidney include: large blood flow, the presence of a variety of xenobiotic transporters and metabolizing enzymes, and concentration of solutes during urine production. In many cases, the conjugation of environmental chemicals to glutathione and/or cysteine targets these chemicals to the kidney where inhibition of renal function occurs through a variety of mechanisms. For example, heavy metals such as mercury and cadmium target the kidney after glutathione/cysteine conjugation. Trichloroethylene and bromobenzene are metabolized and conjugated to glutathione in the liver before renal uptake and toxicity. In contrast, renal injury produced by chloroform and aristolochic acids is dependent on renal cytochrome P450 metabolism to toxic metabolites. Other compounds, such as paraquat or diquat, damage the kidney via the production of reactive oxygen species. Finally, the low solubility of ethylene glycol metabolites causes crystal formation within the tubular lumen and nephrotoxicity. This chapter explores mechanisms of nephrotoxicity by environmental chemicals, using these example compounds. What remains to be accomplished and by far the most difficult process is the elucidation of the detailed mechanisms of tubular cell injury after toxicant uptake and metabolism. The large number of individuals experiencing a decline in renal function with age makes the search for these mechanisms very compelling.

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HISTORICALLY, toxicologic events have brought to light the importance of controlling the levels of naturally occurring and manmade environmental chemicals in our food, air, and water. Environmental pollutants can be emissions, discharges, or accidental releases of chemicals whereas environmental toxins can be natural products of plants, animals, or microbes. No matter the source, environmental chemicals have the potential to adversely affect human health through the disruption of renal functions. This article discusses several examples of nephrotoxic environmental chemicals and their mechanisms of toxic action.

The adverse effects of dissimilar environmental chemicals on the kidney can be attributed to the anatomic, physiologic, and biochemical features of the kidney. A primary reason for the susceptibility of the kidney to the toxic action of environmental chemicals is the large blood flow and the resulting high concentrations of toxicant delivery to the kidney; renal blood flow comprises 20% to 25% of the cardiac output. The kidney also hosts a variety of organic solute and ion transporters, and xenobiotic metabolizing enzymes that can concentrate and

metabolize toxic compounds and damage cells of the nephron. The ability of the kidney to concentrate urine can result in increased localized concentrations of toxicants and initiate renal dysfunction. Further, compounds with low aqueous solubilities may reach concentrations within the kidney that cause them to precipitate or crystallize within the tubular fluid, leading to obstruction of tubular flow or damage to the integrity of the tubular epithelium. Environmental chemicals concentrated by the kidney may contribute to calculus formation and the development of associated renal pathologies.

Several classes of dissimilar toxicants target the kidney. Among them are therapeutic agents such as antibiotics, antineoplastics, anesthetics, diuretics, immunosuppressants, radiocontrast agents, and nonsteroidal anti-inflammatory drugs. Other nephrotoxic compounds include heavy metals, halogenated aliphatic hydrocarbons, herbicides/fungicides, mycotoxins, plant alkaloids, organic solvents, and volatile hydrocarbons such as petroleum fuels. Many of the latter classes of compounds exist as industrial pollutants and natural products.

HEAVY METALS

Mercury

Mercury, like cadmium, gold, lead, nickel, chromium, and uranium, is a nephrotoxic metal.¹ Mercury can exist in 3 oxidation states: elemental mercury (Hg^0), mercurous mercury (Hg^{1+}), and

From the Department of Pharmaceutical Sciences, Medical University of South Carolina, Charleston, SC.

Address reprint requests to Rick G. Schnellmann, PhD, Department of Pharmaceutical Sciences, Medical University of South Carolina, 280 Calhoun St, PO Box 250140, Charleston, SC 29425. E-mail: schnell@musc.edu

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mercuric mercury (Hg^{2+}). Hg^0 is a ubiquitous environmental pollutant introduced primarily by degassing of the earth's crust and is oxidized to Hg^{2+} in mammalian cells.² Organomercurials, such as methyl mercury, are produced by microbial metabolism of both Hg^0 and Hg^{2+} .³ Organomercurials are hydrophobic and readily cross lipid membranes. Interestingly, the hydrophilic inorganic mercuric salts produce a greater degree of renal injury and exhibit decreased neurotoxicity compared with organic mercury compounds.⁴

Humans may be exposed to various types of mercury via numerous routes. Organic mercury enters the food chain of humans by accumulating in living organisms, such as fish. Other sources of mercury exposure are occupational, industrial waste, the use of organic mercurials as fungicides, and the inhalation of elemental mercury vapor.³

Mercuric chloride nephrotoxicity has been well studied and once was used as a model of acute renal failure.³ The nephrotoxicity is characterized by an initial reduction in renal blood flow and a progressive decline in the glomerular filtration rate. Although blood flow may return to normal within 48 hours, glomerular filtration rate remains reduced for a period of time. Mercuric chloride produces damage to the proximal tubules, primarily the S_3 segment. This damage has been associated with increased Na^{2+} and glucose excretion, and a decrease in anion excretion. Cellular changes reported in the proximal tubules include dysregulation of Ca^{2+} homeostasis, loss of brush border membrane, appearance of vacuoles, and mitochondrial changes consistent with oncosis (necrosis). Protein sulfhydryl groups may represent the initial target in Hg^{2+} toxicity. For example, the binding of Hg^{2+} to the sulfhydryl groups of critical proteins within cells alters their normal function and initiates cellular injury and death.⁵ Interestingly, mitochondrial enzymes appear to be particularly sensitive to Hg^{2+} exposure.

Renal cells possess at least 2 well-known defense mechanisms against Hg^{2+} toxicity.⁶ In both cases, the defense mechanisms take advantage of the high affinity Hg^{2+} has for sulfhydryl groups. Glutathione (GSH) protects from Hg^{2+} exposures by competitively binding free Hg^{2+} . For example, cells that are GSH depleted are more sensitive to Hg^{2+} exposure, whereas cells with increased intracellular GSH are protected from Hg^{2+} exposures.⁶ Another cellular defense mechanism against Hg^{2+}

toxicity is the metal binding protein metallothionein (MT). MT is a low molecular weight protein, rich in cysteinyl residues, with a high affinity for metals.⁷ MT expression is induced in the kidney after exposure to mercuric chloride and MT-knockout mice have confirmed the protective role of MT in mercuric chloride-induced nephropathy.⁸

Although intracellular GSH protects against Hg^{2+} toxicity, it has been shown that plasma GSH and cysteine bind to Hg^{2+} and that Hg conjugates are taken up more rapidly in proximal tubule cells than Hg^{2+} .⁵ The brush border membrane of proximal tubule cells is rich with γ -glutamyltransferase and cysteinylglycinase activities, which convert Hg-GSH conjugates to Hg-cysteine conjugates. These compounds are transported into the tubular cells by the Na^+ -dependent low-affinity L-cysteine, B⁰, and L-alanine, L-serine, and L-cysteine (ASC) systems and the Na^+ -independent L-system.⁹ In contrast to the cytoprotective effects of intracellular GSH, plasma GSH and cysteine mediate Hg^{2+} nephrotoxicity through targeting the Hg^{2+} to the kidney.⁵

Cadmium

Human cadmium exposures occur in the workplace via inhalation of cadmium-containing dusts and fumes or through food consumption. Cadmium has been shown to bioaccumulate, primarily in the kidney, and has a half-life greater than 10 years in humans.¹⁰ Although cadmium-induced acute renal failure can occur in humans, the greater issue is the long-term consequence of renal cadmium accumulation and potential chronic renal function.

Cadmium is a strong inducer of MT, and MT-mediated detoxification of Cd has been shown using MT-transgenic and MT-null mice.⁷ However, Cd-MT formed in the liver paradoxically may result in increased cadmium accumulation in the kidney (Fig 1). In this case, Cd-MT complexes may be formed in the liver and released into the blood slowly or after liver injury. Cd-MT is filtered by the glomeruli and is taken up into the proximal tubule cells by endocytosis.¹¹ Endocytosed Cd-MT is degraded by lysosomes releasing intracellular cadmium, which binds subcellular targets and induces proximal tubular MT expression and toxicity. Although MT expression causes increased Cd accumulation in the kidney, MT-null mice are more sensitive to cadmium-induced nephrotoxicity.¹² However, there also is evidence that GSH

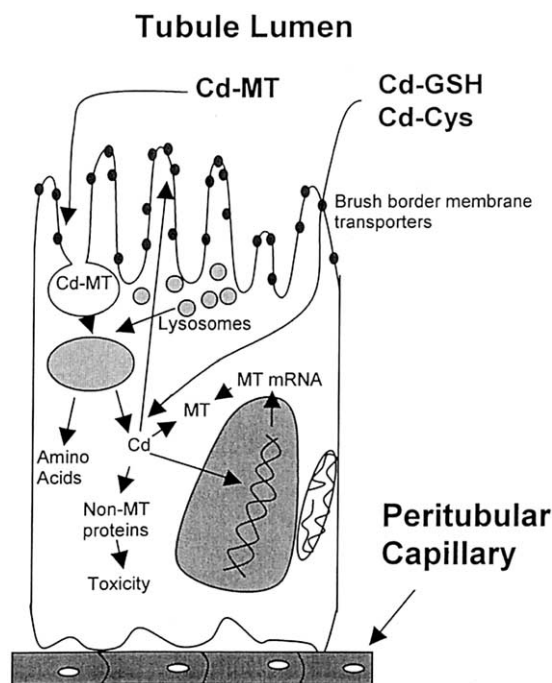


Fig 1. Uptake of Cd-MT, Cd-GSH, and Cd-Cys complexes by proximal tubule cells. Filtered Cd-MT is reabsorbed via endocytosis and degraded by lysosomes. Free Cd induces MT synthesis and interacts with cellular protein targets, causing toxicity. Cd-GSH and Cd-Cys are transported via brush border membrane transporters. Adapted with permission from Goldstein and Schnellmann.²¹

and cysteine conjugates of cadmium are taken up more readily than cadmium in renal cells and that these conjugates may play an important role in cadmium nephrotoxicity.¹³ This is consistent with observations that many renal toxicants selectively accumulate in the kidney as GSH or cysteine conjugates formed outside the kidney.

Cadmium-induced nephrotoxicity in mice is characterized by increased urinary excretion of glucose and γ -glutamyltransferase and increased blood urea nitrogen.¹² Cadmium exposure causes kidney enlargement, degeneration of the proximal convoluted tubule, and glomerular swelling. Several Na^+ -dependent brush border membrane transporters are inhibited by inorganic cadmium including: phosphate, glucose, and amino acids. This may explain some of the symptomology of Cd exposure such as proteinuria, phosphaturia, glucosuria, aminoaciduria, and polyuria. It still is unclear, however, whether inhibition of brush border membrane transporters is caused by direct interaction of

Cd^{2+} with the transporters, loss of brush border membrane integrity, or both. Similar to Hg^{2+} , the mechanism(s) Cd^{2+} induced proximal tubule cellular injury and death have not been elucidated.

HALOGENATED HYDROCARBONS

Trichloroethylene

Trichloroethylene (TCE) is a widely used industrial solvent and a common environmental contaminant. Although TCE exposures may come from contaminated drinking water, higher-level exposures are more likely to originate from occupational exposures. Although the kidney is not a selective target of TCE directly, S-(1,2-dichlorovinyl)-L-cysteine (DCVC), a biotransformation product of TCE, is a nephrotoxicant in several mammalian species. DCVC offers an additional example of how GSH and cysteine conjugation can lead to the transport of toxicants to the kidney, and ultimately, nephrotoxicity (Fig 2).

Conversion of TCE to DCVC is mediated partly by glutathione S-transferases, which conjugate TCE with GSH, producing S-(1,2-dichlorovinyl) glutathione. Although this step takes place primarily in the liver, some conjugation may take place in the target organ as well.¹⁴ Subsequent biotransformation may occur in the liver, gastrointestinal tract, and kidney. Ultimately, the S-(1,2-dichlorovinyl)-GSH, cysteine, or N-acetylated cysteine conjugates are transported into the epithelial cells of the renal proximal tubules. Within the proximal tubular cells, DCVC, the penultimate nephrotoxicant, is a substrate for β -lyase activity, which produces the reactive electrophile S-(1,2-dichlorovinyl) thiol. It is thought that S-(1,2-dichlorovinyl) thiol binds covalently to cellular nucleophiles such as proteins or DNA and initiates cell injury and death.

DCVC-mediated nephrotoxicity produces symptoms typical of acute renal failure. For example, male F344 rats exposed to DCVC exhibit increased blood urea nitrogen levels and urinary excretion of glucose.¹⁵ Isolated perfused rat kidneys exposed to DCVC (0.1-2.5 mmol/L) exhibited alterations in all urinary parameters (eg, protein, alkaline phosphatase, and γ -glutamyltransferase excretion).¹⁶ The most sensitive parameter was glucose reabsorption, which was inhibited completely at 0.1 mmol/L DCVC. In addition, DCVC administered in the drinking water of male Swiss-Webster mice

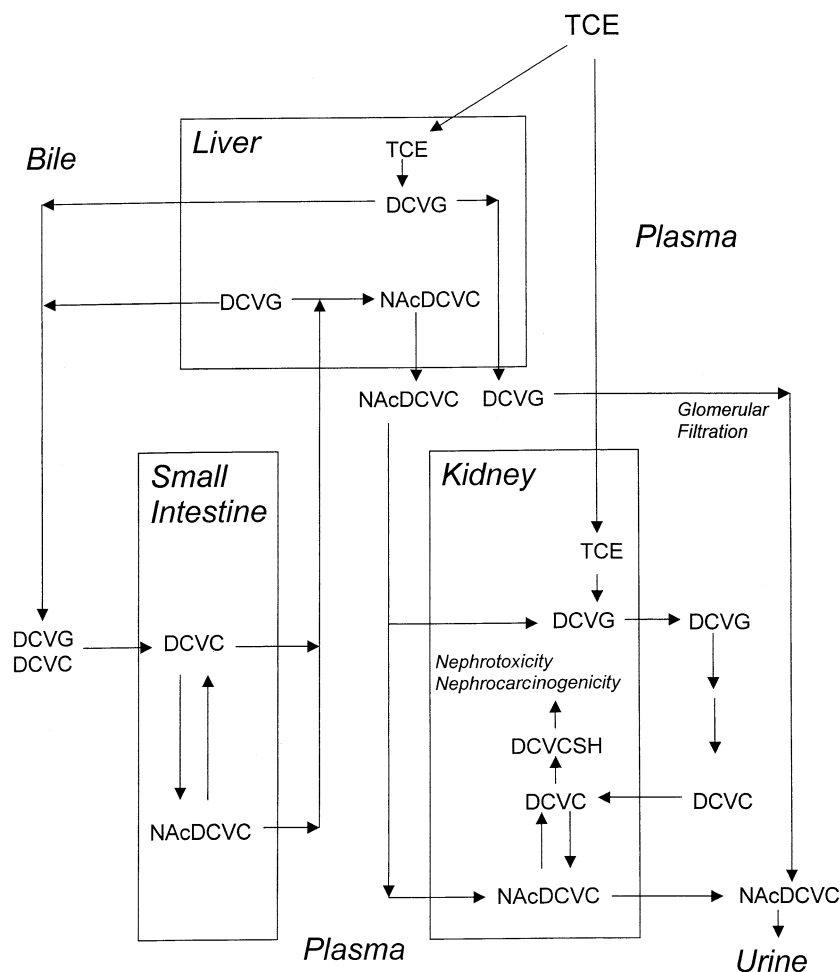


Fig 2. Schematic presentation of interorgan processing of TCE by the GSH-conjugation pathway. DCVG, S-(1,2-dichlorovinyl) glutathione; DCVCSH, S-(1,2-dichlorovinyl) thiol; NAcDCVC, N-acetyl-1,2-dichlorovinyl cysteine. Adapted from Lash, 2000 (public domain).¹⁴

retarded growth by 21 weeks and caused cytomegaly, nuclear hyperchromatism, and multiple nucleoli in the proximal tubules by 21 weeks.¹⁵ Tubular atrophy and interstitial fibrosis also have been observed after DCVC exposure in mice.

The ability of DCVC metabolites to bind DNA has led to studies that examined the carcinogenicity of TCE and its metabolites. Lifetime bioassay studies revealed renal tumors in rats exposed to TCE by gavage or inhalation, although mice and hamsters appear to be resistant to the formation of these tumors.¹⁷ Epidemiology in humans is less conclusive. One risk assessment study, performed by the US Environmental Protection Agency, concluded there was some evidence suggesting that DCVC is mutagenic, but more evidence was needed to determine conclusively if DCVC caused mutations leading to the formation of human tumors. They further concluded that it was unlikely

that TCE directly caused mutations leading to human tumors.¹⁸

Chloroform

Chloroform (CHCl_3) requires biotransformation to produce nephrotoxicity and CHCl_3 exhibits significant susceptibility differences between species and sexes as a result of differences in renal cytochrome P450 (CYP450)-mediated reactive intermediate formation. Whereas hepatic toxicity is similar between both sexes, only male rats and mice develop renal toxicity after CHCl_3 exposure.¹⁹ Early studies of this phenomenon showed that castration before exposure decreased CYP450 levels and afforded resistance to male mice, and pretreatment of female mice with testosterone increased both general CYP450 content and renal susceptibility to CHCl_3 .¹⁹ More recent work has shown that CYP 2E1 appears to be responsible for

the bulk of CHCl_3 activation in the liver and kidney of mice.²⁰ For example, CYP 2E1 (-/-) mice were resistant to CHCl_3 toxicity, whereas CYP 2E1 (+/+) mice were sensitive. Further, inhibition of CYP450 activity with 1-aminobenzotriazole protected CYP 2E1 (+/+) mice from CHCl_3 exposures. Phosgene, a CYP450 product of CHCl_3 , binds proteins and is thought to initiate renal cell injury by this mechanism. Thus, CHCl_3 is one of a few cases of renal CYP450-mediated nephrotoxicity.

CHCl_3 primarily targets the proximal tubules and is characterized by proteinuria, glucosuria, and increased blood urea nitrogen.²¹ CHCl_3 exposures lead to increased kidney weight, fatty degeneration, swelling of the tubular epithelium, the formation of tubular casts, and marked necrosis of the proximal tubules.

CHCl_3 is an animal carcinogen and a suspected human carcinogen, which induces cancer by a non-genotoxic-cytotoxic mode of action. Because of the lack of human epidemiologic evidence, the US Environmental Protection Agency classifies CHCl_3 as a B₂ carcinogen (probably human carcinogen).

A source for human CHCl_3 exposure is drinking water. Chlorination of water for disinfection is inexpensive and effective, however, it results in the formation of several trihalomethanes, including CHCl_3 . Several studies have produced evidence that aqueous CHCl_3 vapors result from hot water usage in the household, and therefore inhalation may represent another route of exposure.^{22,23} CHCl_3 also is used industrially as a solvent, degreaser, and synthetic intermediate, producing workplace exposures.

Bromobenzene

Bromobenzene is a common component of motor oils, and has been used as a solvent and intermediate in industrial chemical syntheses. These uses have led to occupational exposures, dermal and inhalation, and the release of bromobenzene into the environment as a contaminant.

Although the kidney and liver are target organs of bromobenzene, liver biotransformation of bromobenzene is critical for the expression of nephrotoxicity.²⁴ Bromobenzene can be oxidized to several metabolites, including 2-bromophenol, and 2-bromohydroquinone and 2-bromoquinone, which are converted to mono- and diglutathione conjugates.²⁵ Glutathione conjugates of bromohy-

droquinone are at least 1,000-fold more nephrotoxic than bromohydroquinone. GSH conjugates of bromohydroquinone are further biotransformed to N-acetyl-cysteine conjugates, which may undergo β -elimination via cysteine conjugate β -lyase or oxidation, leading to arylation of cellular nucleophiles.²⁵ Once again, bromobenzene is another example of a toxicant that requires metabolism to a GSH conjugate to produce nephrotoxicity.

The proximal tubule epithelium, primarily the S3 segment, is the major site of toxic action for bromobenzene. For example, Rush et al²⁶ showed that bromobenzene significantly increased blood urea nitrogen, and significantly inhibited the accumulation of the organic anion *p*-aminohippurate and organic cation tetraethyl-ammonium. Acute toxicity also is characterized by proteinuria, enzyuria, and glucosuria.

HERBICIDES

Paraquat/Diquat

Paraquat and diquat are structurally similar non-selective herbicides. When used properly these compounds offer no significant risk to humans, partly because the intact skin provides a significant barrier against penetration. However, most poisonings occur from accidental ingestion or in cases of attempted suicide. Interestingly, diquat solutions as low as 1% have resulted in human toxicity.²⁷ When ingested, these compounds cause multisystem toxicity to the lung, kidney, heart, and central nervous system.

Both paraquat and diquat are nephrotoxic, acting primarily on the proximal tubules. A recent study²⁸ showed evidence that the mechanism of paraquat cellular uptake in baboon proximal tubule cells was via the polyvalent organic cation transporter. For example, paraquat uptake was inhibited competitively by cimetidine, a drug taken up by this transport mechanism.

Patients poisoned by paraquat develop acute tubular necrosis resulting in elevated blood urea nitrogen and decreased creatinine clearance.²⁹ Abnormal urine analysis, such as urinary red and white blood cells and proteinuria, also has been associated with paraquat poisoning. Symptoms of paraquat/diquat poisoning may be delayed for up to 48 hours after ingestion in humans.

Paraquat and diquat produce toxicity in renal proximal tubular cells through the generation of

reactive oxygen species. Reactive oxygen species cause lipid peroxidation of membranes, leading to loss of membrane integrity and cell death. Reactive oxygen species also alter cellular nucleophiles such as proteins, leading to dysfunctional enzymes, and cause modification of DNA bases. The observation that depletion of glutathione significantly enhances the toxicity of paraquat is further evidence that paraquat targets cellular nucleophiles.³⁰

ORGANIC SOLVENTS

Ethylene Glycol

Ethylene glycol (EG) is an antifreeze in cooling systems, a component of hydraulic brake fluid, an ingredient in chemical synthesis, and a solvent. Further, EG also has been used to de-ice airplanes and runways. Life-threatening human exposures to EG generally occur from ingestion of large quantities in attempted suicides. Dogs and cats, 2 species prone to accidental EG poisonings,³¹ have shown signs of nephrotoxicity after ingestion of mishandled EG sources.

EG-mediated renal toxicity requires the metabolic transformation of EG (Fig 3). EG metabolism takes place primarily in the liver via alcohol dehydrogenase, which transforms EG to glycoaldehyde and the organic acids glyoxylic and oxalic acid.³² When oxalic acid is concentrated in the urine, calcium oxalate crystals form leading to crystalluria and nephrolithiasis. For this reason, EG poisoning has been used as a model for the study of renal crystal deposition. Oxalic acid also is present in foods such as tomatoes, garlic, spinach, and tea, and individuals consuming dietary excesses of these foods may develop mild calcium oxalate crystalluria without associated renal insufficiency.

Symptoms associated with EG poisoning include metabolic acidosis, crystalluria, nephrolithiasis, low specific gravity of urine, proteinuria, and microscopic hematuria. These symptoms are similar to the clinical condition known as primary hyperoxaluria, a rare inherited metabolic disorder associated with early onset renal failure and death. EG-induced crystal deposition has been detected in the proximal tubules where crystals have been detected unbound in the lumen and attached to the surface of epithelial cells.³³ Calcium oxalate crystals also have been detected in the lumina of the distal tubules and collecting ducts after EG exposure. Crystal formation leads to obstruction, hin-

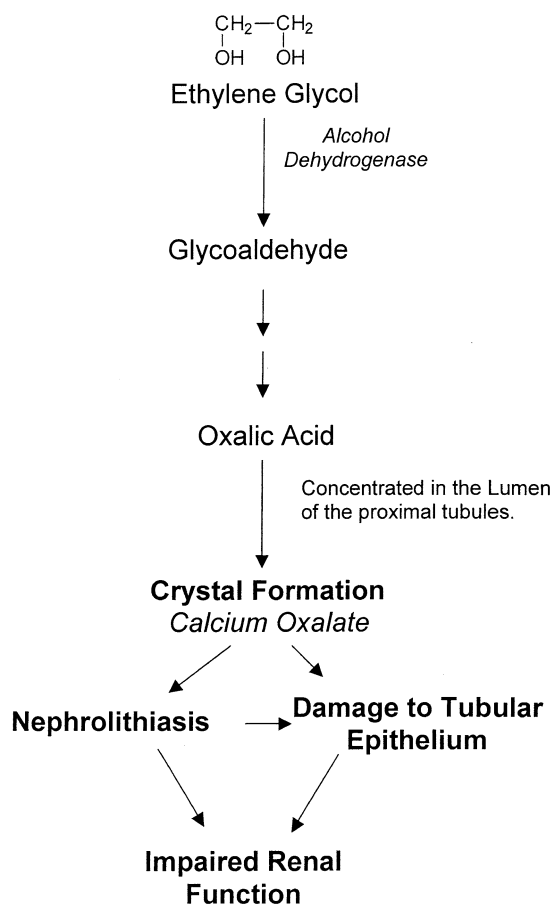


Fig 3. Proposed mechanism of EG-mediated renal dysfunction.

ders renal function, and causes chronic abacterial interstitial nephritis with glomerulosclerosis, tubular atrophy, and interstitial fibrosis.

NATURAL PRODUCTS

Herbal Remedies

Aristolochic acids, plant alkaloid products of the Chinese herb *Aristolochia fangchi*, are nephrotoxic. Between 1990 and 1992, renal failure developed in young Belgian women who were on a slimming regimen containing Chinese herbs. The rapidly fibrosing nephropathy is now described as Chinese herbs nephropathy (CHN). About 100 cases of CHN have been identified in Belgium, with approximately half of them requiring renal transplantation.³⁴ In 1994, the presence of aristolochic acids in diet pills, instead of tetradrine, confirmed suspicions that *Stephania tetrandra* had

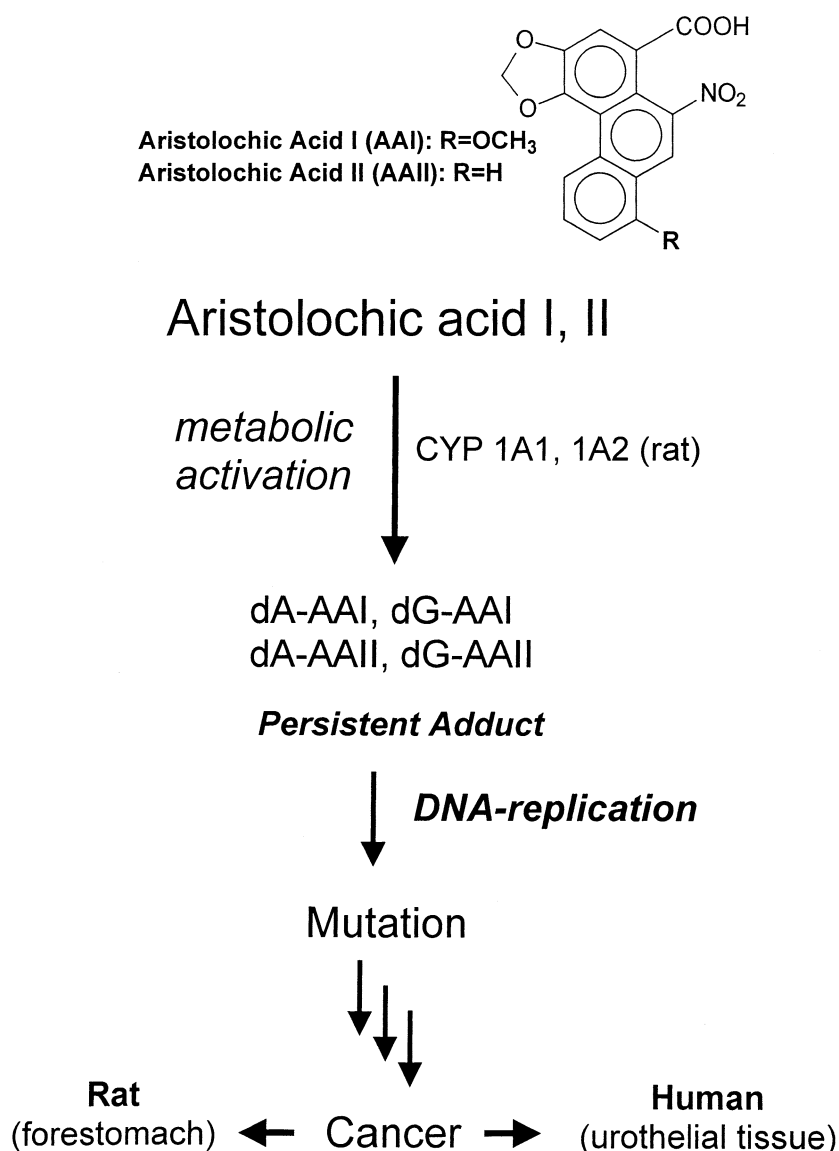


Fig 4. Postulated mechanism for the carcinogenicity of aristolochic acid in humans and rodents. 7-(deoxyadenosin- N^6 -yl) aristolactam I (dA-AAI); 7-(deoxyguanosyl- N^2 -yl)aristolactam I (dG-AAI); 7-(deoxyadenosin- N^6 -yl) aristolactam II (dA-AAII); 7-(deoxyguanosyl- N^2 -yl) aristolactam II. Adapted with permission from Arlt VM, Stiborova M, Schmeiser HH: Aristolochic acid as a probable human cancer hazard in herbal remedies: A review. *Mutagenesis* 17:265-277, 2002 by permission of Oxford University Press.³⁵

been replaced by *A. fangchi* in the herbal formulation. The nephropathy produced by aristolochic acids is characterized by extensive interstitial fibrosis and tubular proteinuria.

One proposed mechanism for the nephrotoxicity produced by aristolochic acid is DNA-alkylation (Fig 4). The major components of aristolochic acids, aristolochic acid I (AAI) and II (AAII), are mutagens. Both compounds are nitrophenanthrene carboxylic acids that must be activated metabolically to the ultimate mutagenic intermediate. AAI and AAII form DNA adducts in vitro. The major adduct species identified are 7-(deoxyadenosin- N^6 -

yl) aristolactam I (dA-AAI), 7-(deoxyguanosyl- N^2 -yl) aristolactam I (dG-AAI), 7-(deoxyadenosin- N^6 -yl) aristolactam II (dA-AAII), and 7-(deoxyguanosyl- N^2 -yl) aristolactam II.³⁴ These structures indicate that a cyclic N-acylnitrenium ion with a delocalized positive charge is the ultimate carcinogenic species. Preferential binding to the exocyclic amino groups of purine nucleotides is followed by hydrolysis to the corresponding 7-hydroxyaristolactam. Therefore, the proposed metabolic activation of AAI and AAII is via conversion to N-hydroxyaristolactams I and II followed by formation of aristolactam-nitrium ions, which al-

kylates purine nucleotides. Rat hepatic microsomal activation of AA has been attributed to CYP450 1A1 and 1A2.

Specific aristolochic acid–DNA adducts have been detected in the kidney and ureter of CHN patients.³⁵ Increased incidence of urothelial cancers also is associated with CHN. About 40% of CHN patients with end-stage renal failure show evidence of urothelial cancer. Aristolochic acid produces primary tumors of the forestomach, renal cortex, renal pelvis, and urinary bladder, and is acutely nephrotoxic at higher doses.³⁴

SUMMARY

Because of the unique anatomy, biochemistry, and physiology of the kidney, it is the target of numerous environmental chemicals. The toxicants discussed in this article show several mechanisms by which the kidney is targeted by xenobiotics. The ability of the kidneys to selectively accumulate GSH-conjugate species of chemicals such as TCE, bromobenzene, and mercury make it the target of these toxicants and various drugs. What remains to be accomplished and by far the most difficult process is the elucidation of the detailed mechanisms of renal proximal tubular injury after uptake or biotransformation. Separating specific effects of these toxicants on cellular function and biochemistry, which may not be involved in cell injury and death, from those that are remains a daunting task. The large number of patients experiencing significant renal functional decline without obvious cause makes the search for these mechanisms even more compelling.

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