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REVIEW ARTICLE

# Environmental injury to the kidney: Interstitial nephritis



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## KEYWORDS

environmental toxins;  
interstitial nephritis;  
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**Summary** The First Emperor of China (Qin Shi Huang: 259–210 BCE) would have been interested in interstitial nephritis. He might conceivably be fascinated to know that consumption of mercury elixir, instead of giving him immortality, might have shortened his life by giving him interstitial nephritis. In the Balkan region of Eastern Europe, clustering of a peculiar interstitial nephritis is prevalent. One environmental risk contributing to *Balkan endemic nephritis* is aristolochic acid contamination of cooking flour, drinking water, and herbal medicine. In addition, the popular use of nonprescription Chinese weight reduction herbs and public unawareness of the consequential aristolochic acid nephropathy has become a worldwide problem. Finally, the mighty Romans of antiquity lost their empire, arguably due to lead in their wine containers, lead water pipes, and lead cooking utensils. In modern times, lead paint has become universally banned, which has resulted in a reduction of lead-induced interstitial nephritis. In recent decades, bisphenol A (BPA) has been identified as a new environmental risk. BPA is in the plastic coating of food and beverage containers to prevent corrosion. BPA is so ubiquitous that urinary BPA and proteinuria are present in a high percentage of the population. BPA-induced kidney injury and other health concerns have led certain countries to ban BPA. Now, BPA-free containers are being introduced with great fanfare by manufacturers, but safety issues on all plastic products remain. It begs the question whether “plastics” of today take the place of “lead” in ancient Rome. This is a challenging question without an answer at this point.

中國的首任皇帝（秦始皇：259BCE–210BCE）應該會對以下事實感到有興趣——他眼中的長生不老丹藥（含水銀），原來會導致間質性腎炎，令他反而會折壽。另外，在東歐的巴爾幹地區，一種獨有的間質性腎炎頗為盛行，此種「巴爾幹流行性腎炎」歸因於環境性因素——馬兜鈴酸（aristolochic acid）污染了食用麵粉、飲用水、及草藥。事實上，基於大眾對馬兜鈴酸腎病變缺乏認識，非處方中草藥（減重用）的普遍使用已導致了全球性的健康問題。有人甚至指出，羅馬帝國

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的覆亡，可能與鉛中毒有關（酒容器、水管、煮食用具中普遍含鉛）。近代，含鉛顏料已全面被禁止，減少了鉛所導致間質性腎炎的發生。在最近數十年，bisphenol A (BPA) 被發現為一種新的環境性危害，它存在於食物與飲料容器上的塑料塗層，用於預防腐蝕，其廣泛使用導致人口中有高比例出現尿液含 BPA 及蛋白尿現象。基於與 BPA 有關的腎臟傷害及其他健康問題，BPA 已被某些國家禁止使用。目前，有生產商正致力推廣不含 BPA 的容器，但塑膠製品的安全性問題仍然存在。現代塑料的危害是否類似古羅馬時代的鉛，實在是一個值得令人深思的課題。

## Introduction

The timeline of the early Han dynasty parallels that of the ancient Roman Empire of the Mediterranean world. Both the Roman and Han empires—at their respective pinnacles—were about equal in population, wealth, and cultural and political supremacy. Each of these empires declined and collapsed due to multiple reasons of their own. For the Roman Empire, the contamination from lead cooking utensils; lead conduits in transportation of drinking water and storage of their wine have been regarded as a possible issue. If correct, it is an early example of environmental pollutants on the fate of an empire.

## New environmental risk: Bisphenol A and kidney injury

With reference to environment and kidney injury, there has been increasing scientific and public concern about bisphenol A (BPA), an industrial ingredient of polycarbonates, coating food and beverage containers used to prevent corrosion. BPA is an endocrine disruptor mimicking estrogen and disrupting glucose, thyroid, adipose tissue metabolism, and increasing diabetes mellitus, infertility, and cardiovascular risks.

Human exposure to BPA is so ubiquitous that it is detected in the urine of 95% of the population in industrialized countries. Two recent *Kidney International* publications<sup>1,2</sup> focused a bright light for the first time on possible kidney injury from BPA. The first paper was in late 2012: in over 3000 adult residents of Shanghai, China increasing urinary BPA was documented and shown to be associated with increasing proteinuria.<sup>1</sup> This association stayed unmodified by age, sex, body mass index, hypertension, or sociodemographic factors of alcohol consumption or smoking.

In early 2013, similar association of urinary BPA to urinary proteinuria was demonstrated in over 700 children<sup>2</sup> from analysis of samples in a biorepository of the United States 2010 National Health and Nutrition Examination Survey.<sup>2</sup> How the medical community and the general public will respond to this line of new findings is an open question. With BPA the focus of swiftly rising public concern, BPA-free products are being introduced with great fanfare by the manufacturers of plastic utensils.

## Historical perspectives

With lead arguably weakening the ancient Roman Empire as historical background, the ubiquitous usage of plastics in our modern life, begs the question whether “plastics” are

the environmental risks to today’s world as “lead” was to the ancient Roman world. The following historic perspective reflecting on environmental risks to kidney injury is relevant and compelling—particularly in relation to how interstitial nephritis came to be defined and understood.

In 1842, Bowman’s<sup>3</sup> examination of kidney histology led to his discovery of Malpighian bodies (or glomerular capsules) being connected to kidney tubules. He suggested that the filtration of urine resulted from this assembly. Later histologists regarded the interstitium of the kidney, as 80% of the renal parenchyma exclusive of the glomerular compartment. Subsequently, the term “interstitial nephritis” is commonly used to refer to kidney injury of the interstitium, and distinct from predominantly glomerular injury, which is referred to as glomerulonephritis.

In 1860, Taylor and Pavey<sup>4</sup> described interstitial injury following mercury bichloride ingestion. Those readers of this commentary with an interest in history will easily recall that the great Han dynasty historian Sima Qian, recorded that Qin Shi Huang, the First Emperor of a unified China, took mercury as an elixir for everlasting life. If so, mercury poisoning may have shortened the Emperor’s life to 49 years (259–210 BCE). It can be argued that the emperor Qin Shi Huang may have been the first world figure to have his life cut short by mercury-induced interstitial nephritis.

In 1898, Councilman<sup>5</sup> observed in victims of diphtheria or scarlet fever, that despite sterile kidneys—with evidence of bacterial infection—there was intense leukocyte infiltration into the interstitium, features compatible with an allergic reaction. Hence the concept evolved that interstitial nephritis was an allergic reaction to infections such as diphtheria or scarlet fever.

In 1943, Melnick<sup>6</sup> reported similar findings in the kidney of allergic reaction with antibiotics. In 1953, Spuhler and Zollinger<sup>7</sup> reported that analgesics can cause interstitial nephritis.

Thus, the historical list of conditions causing interstitial nephritis includes contamination with heavy metal such as mercury, exposure to infections such as diphtheria or scarlet fever, and allergic reaction to antibiotics and analgesics.

## Acute interstitial nephritis

In addition to the historical perspectives above, the list of conditions giving rise to acute and chronic interstitial nephritis continues to expand rapidly. Acute interstitial nephritis is characterized by renal parenchymal edema and infiltration of inflammatory cells.

Acute interstitial nephritis can result from the following general categories of injury: antibiotics; nonsteroidal anti-inflammatory drugs; diuretics; infectious agents; analgesics; autoimmune reactions.

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