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ENVIRONMENTAL TOXICANTS IMPLICATED IN THE ETIOLOGY OF BALKAN ENDEMIC NEPHROPATHY: MOLECULAR MECHANISMS OF THEIR TOXICITY AT THE CELLULAR LEVEL

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Balkan Endemic Nephropathy (BEN) is a slowly progressing, familial, chronic, noninflamatory bilateral lesion of the entire urinary tract, that affects rural populations in several circumscribed areas of the Balkans [1]. The disease has no acute onset, runs asymptomatically and progresses slowly for many years, until the patient presents with the clinical symptoms and signs of advanced renal failure. Clusters of BEN cases are found in villages situated mainly in the alluvial plains along tributaries of the Danube River in Bosnia, Croatia, Serbia, Bulgaria, and Romania [1, 2]. A study describing the time trend of the incidence of BEN in villages of the Vratza district, Bulgaria, suggests that after the initial peak, the incidence remained quite stable, and declined after 1984 [3, 4].

Urinary tract tumors (UTT) occur at a higher frequency in BEN patients than in the average population [5]. Of all BEN patients, 2-47% have UTT [6], and recent large epidemiological studies show that people in endemic BEN areas are at a very high relative risk for UTT [7] as compared to inhabitants in non-endemic areas. The high association between UTT and BEN may signify a common causative agent(s).

Although the **etiology of BEN ant its related UTT** is still inconclusive, experts now concede that the disease may result from prolonged exposure to a multitude of environmental toxicants, such as ochratoxin A (OTA), polynuclear aromatic hydrocarbons (PAH), arsenic, etc. [8, 9, 10]. The OTA, PAH, and arsenic, could operate individually, or simultaneously, and, in predisposed individuals, may result in genotoxic and/or epigenetic effects, and in nephropathy/neoplastic outcomes under certain conditions. In this review we are focusing on the molecular mechanisms of toxicity of three environmental toxicants implicated in the etiology of BEN - OTA, PAH, and arsenic.