

also observed between exposure to artesian well water and cancer of the bladder, lung, and liver.¹¹

A cohort study was conducted on lower urinary tract cancers in the 3 high-risk villages of Ho-Mei, Fu-Hson and Hsin-Ming including a total of 2258 residents born before 1959. Cox's proportional hazards regression analysis of multiple risk factors associated with bladder cancer showed a statistically significant association between arsenic exposure which existed in artesian well water and risk of low urinary cancer.¹²

Causative Factors of Urinary Cancer in the BFD Endemic Area

In order to investigate the possible causative factors of urinary cancer in the BFD endemic area, a retrospective, questionnaire study of bladder carcinogenesis was performed. Two groups of bladder cancer patients, one from the BFD endemic area and the other group from elsewhere in Taiwan with matching residents in the same living area as controls was performed. The statistical analysis showed that drinking deep well water was the only significant factor for patients with bladder cancer from the endemic area.¹³

The association between consumption of artesian

well water and skin cancer, internal cancer, including bladder, kidney, lung, and liver, and colon had been documented since the 1960s. Urinary cancers had the highest relative risks. The high content of arsenic and the high concentration of a "fluorescent substance" in artesian well water in this area were the only 2 related factors identified so far. In 1975, Dr. Lu discovered fluorescent compounds in the endemic well water;¹⁴ and he isolated and purified the fluorescent humic substances in the subsequent few years. These humic substances contained a large number of elements (among which is arsenic) (Fig. 3), and could develop blackfoot disease in an animal model.¹⁵ When the incidence of bladder cancer in 19 villages and districts in the BFD endemic area was compared with the fluorescence intensities of water samples from wells, a dose correlation was found. The similarity of the spectral fingerprints of the fluorescent compounds suggests a common source for these materials. The fluorescent compounds could also be connected with the high incidence of bladder cancer.¹⁶

The fractions of the fluorescent substance isolated from the endemic well water were tested for mutagenicity with the Ames screening test using *Salmonella typhimurium* TA100 (base replacement test) and TA 98 (frame-shift test). However, phthalate and humic acid, the major compounds of the fluorescent substances can not induce any pathological changes in the urinary bladder of rats. Including arsenic in the food for rats, caused remarkable inflammatory changes of the bladder epithelium with bladder stone formation; but it was not like the bladder cancer of rats induced by feeding with 0.05% BHBN.¹⁷ Up to now, neither humic acid nor arsenic has been proved to be a urinary carcinogen by animal experiments in the literature.¹⁸ Yet recent molecular studies support arsenic having some mechanistic relation with urothelial carcinogenesis.¹⁹ Arsenic increases chromosomal breaks, sister chromatid exchanges, and morphological transformations in mammalian cells, although it is not mutagenic by itself.²⁰ It is likely that inorganic arsenic compounds act as cocarcinogens rather than primary carcinogens in vivo as well as in vitro.²¹

Arsenic in Well Water and Incidence of Urinary Cancer

Recent epidemiological and ecological studies

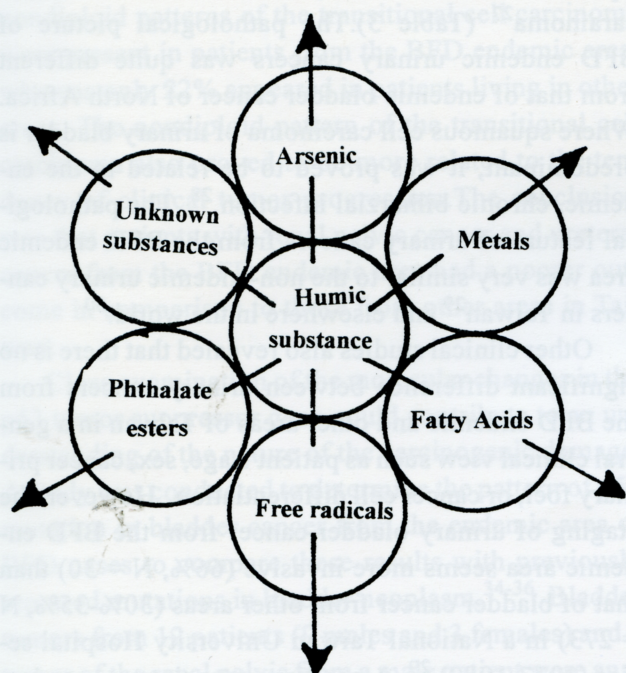


Fig. 3. Schematic representation of the multiple action of the fluorescent humic substances on organisms.