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Assessment of the cytotoxic and mutagenic potential of the Jialu River and adjacent groundwater using human-hamster hybrid cells

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ABSTRACT

The Jialu River in China has been seriously polluted by the direct discharge of industrial and domestic wastewater. The predominant contaminants of the Jialu River and its adjacent groundwater were recently investigated. However, the potential genotoxic impact of polluted water on human health remains to be clarified. Here, we used human–hamster hybrid (A_L) cells, which are sensitive for detecting environmental mutagens. We found that the cytotoxicity and mutagenicity of the groundwater in the Jialu River basin were influenced by the infiltration of the Jialu River. Hydrological periods significantly affected the cytotoxicity, but not the mutagenic potential, of surface and groundwater. Further, the mutagenic potential of groundwater samples located <1 km from the Jialu River ($S_{M\text{-}2}$ water samples) was detected earlier than that of groundwater samples located approximately 20 km from the Jialu River (S_N water samples). Because of high cytotoxicity, the mutagenic potential of water samples from the Jialu River ($S_{M\text{-}1}$ water samples) was not significantly enhanced compared with that of untreated controls. To further assess the mutagenic dispersion potential, an artificial neural network model was adopted. The results showed that the highest mutagenic potential of groundwater was observed approximately 10 km from the Jialu River. Although further investigation of mutagenic spatial dispersion is required, our data are significant for advancing our understanding of the origin, dispersion, and biological effects of water samples from polluted areas.

Introduction

Accidental pollution of surface water occurs frequently worldwide, and rivers act as the most important medium for the transportation of environmental pollutants and transformation (White and Rasmussen, 1998; Ohe et al., 2003, 2004). The United States Environmental Protection Agency (USEPA)'s Toxic Release Inventory reported that approximately 0.1 billion

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kilograms of chemical pollutants were directly released into surface water in 2014 (USEPA, 2016). Moreover, airborne emission and surface runoff are largely responsible for the transport of chemical pollutants to aquatic systems (Motelay-Massei et al., 2006). In contrast, chemical pollutants in surface water are readily soluble and move slowly through layers of soil, sand, and rocks and may be subject to transport into other media such as groundwater (Mehler et al., 2010; Chen et al., 2012; Ma et al., 2013). The latter is important for agricultural, recreational, and domestic activities, particularly as a source of drinking water in most parts of the world (Wang et al., 2011). Numerous studies assessed the potential risk of the adverse effects of polluted surface and groundwater on human health (Fries and Puttmann, 2004; Nakada et al., 2008; Ma et al., 2012b). In addition, disinfection by-products (DBPs), formed by the reaction of disinfectants with natural organic matter in surface and groundwater, were also considered to be cytotoxic and genotoxic (Richardson and Postigo, 2015; Wagner and Plewa, 2017). Evidence indicates that the pollution of drinking water is closely related to the mortality rate of patients with esophageal (Zhang et al., 2003), liver (Li et al., 1994), and urothelial cancers (Markovic, 1993). Moreover, the risk to health of polluted drinking water is not solely the sum of the effects of individual compounds. Therefore, there is growing concern for the additive, synergistic, and antagonistic effects of such complex mixtures of pollutants (Wilkinson et al., 2000), particularly the genotoxicity of organic residues in polluted groundwater.

The Jialu River, which is located in Fugou County, Zhoukou City, Henan Province, is 256 km long, and its basin is 5896 km^2. The Jialu River is an important tributary of the Huaihe River, which is seriously polluted by the direct discharge of contaminants associated with economic growth and urbanization, such as industrial and domestic wastewater (Ma et al., 2012a), industrial wastes, and untreated or lightly treated sewage (Zhang et al., 2009). Large numbers of treated and untreated sewage from alongshore cities and villages were estimated to be $25{,}124 \times 10^4$ tons per year from 1996 to 1999, 81% of which were discharged from Zhengzhou city (Xiao et al., 1999). As one of the six most important industrial cities by “the development of central zones” stratagem of the Chinese Government, Zhengzhou City has a long history of textile and metallurgy industries and is therefore regarded to exert a strong impact on surface water quality of the Jialu River basin. In rural areas, the main source of drinking water for many residents living along the river is shallow, untreated groundwater. In this area, the incidence of cancers of the digestive system, such as carcinoma of the esophagus, stomach, and liver during 2004–2006, was 6.1×10^{-4}, which is 1.71-fold higher than that during 1973–1975 (Yang, 2010). Epidemiological studies of verbal accounts of autopsies have shown that mortality rates of patients with digestive cancers are three to four times higher along the Huai River basin compared with those in the control areas (Wan et al., 2011). Nitrosamines and secondary amines, which are mutagenic and carcinogenic (Bogovski and Bogovski, 1981; Eichholzer and Gutzwiller, 1998), are the predominant toxic compounds in the Jialu River and its adjacent groundwater (Ma et al., 2012a). Comparative genotoxicity of nitrosamine in drinking water DBPs showed that genotoxic potencies of five nitrosamine DBPs in *Salmonella typhimurium* and CHO cells showed identical descending rank order for genotoxicity and were highly correlated (Wagner et al., 2012). In addition, Wagner et al. (2014) also found that the genotoxicity of analogous N-nitrosamines and N-nitramines relevant to CO_2 capture present a potential risk for contaminating airsheds and drinking water supplies. Flumequine and nitroarenes are the main contributors to the genotoxicity of adjacent groundwater around the Jialu River because of their high soil permeability and lateral seepage (Ma et al., 2012b). We reasoned therefore that assessing the overall effects of these compounds will be facilitated by investigating the cytotoxicity and genotoxicity of the river water and its adjacent groundwater.

Numerous *in vivo* tests on the genotoxicity of water samples were conducted, particularly using indigenous aquatic organisms such as fish (Bahari et al., 1994; Alsabti and Metcalfe, 1995; Minissi et al., 1996), sea urchins (Hose et al., 1983), mussels (Ericson et al., 2002; Klobucar et al., 2003), oysters (Burgeot et al., 1995), newts (Jaylet et al., 1986; Fernandez et al., 1993), and marine worms (Jha et al., 1995). Nevertheless, because of the insensitivity of aquatic organisms to genotoxic compounds and complexities involved in manipulating these organisms in the laboratory, the application of *in vitro* genotoxic tests of water samples is more helpful for investigating the presence and distribution of genotoxins (Ohe et al., 1993; Eckl, 1995; Schnurstein and Braunbeck, 2001). For example, the Ames test was used to demonstrate a dose-dependent increase of five orders of magnitude in the number of TA98 revertants associated with industrial effluent extracts, as well as a lower but significant increase of three orders of magnitude associated with river water extracts 6 km downstream (Cerna et al., 1996). Blue rayon extracts collected downstream of wastewater treatment plants from the Katsura, Nishitakase, and Kamo rivers induce a higher frequency of sister chromatid exchange in cultured Chinese hamster lung cells than those collected upstream, with and without metabolic activation (Ohe et al., 1993).

Although numerous *in vitro* studies demonstrate the genotoxicity of polluted waters, mutations that play important roles in tumor development are not well documented. Human–hamster hybrid (A_L) cells stably express a single copy of the human chromosome 11, which encodes the *CD59* cell surface antigen, rendering A_L cells sensitive to killing by specific monoclonal antibodies in the presence of rabbit serum complement (Hei et al., 1998). These hybrids were used to detect the mutagenic effects of ionizing radiation (Wu et al., 1999; Hong et al., 2010) and chemicals (Bao et al., 2009; Zhao et al., 2011). For example, a 50-fold increase in mutations at the *CD59* locus occurs compared with the *HPRT* locus in crocidolite-treated A_L cells (Hei et al., 1992). Other studies using this system demonstrated that arsenic, which was considered a serious contaminant of drinking water and a nongenotoxic carcinogen for decades, is actually a strong mutagen (Jacobson-Kram and Montalbano, 1985; Lee et al., 1985; Hei et al., 1998; Kessel et al., 2002). Similarly, the mutagenicity of cadmium (Filipic and Hei, 2004) and asbestos fibers (Xu et al., 1999, 2002) in contaminated environmental compartments (sediment, water, and air) was demonstrated using the A_L mutagen detection system. Meanwhile, using the Ames test, raw water and drinking water samples from

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