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ScienceDirect
Mutation Research 626 (2007) 143–154
Genetic Toxicology and Environmental Mutagenesis
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Perturbation of cytochrome P450, generation of oxidative stress and induction of DNA damage in *Cyprinus carpio* exposed *in situ* to potable surface water

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Received 15 December 2005; received in revised form 27 September 2006; accepted 28 September 2006
Available online 1 December 2006

Abstract

Epidemiological evidence suggests a link between consumption of chlorinated drinking water and various cancers. Chlorination of water rich in organic chemicals produces carcinogenic organochlorine by-products (OBPs) such as trihalomethanes and haloacetic acids. Since the discovery of the first OBP in the 1970s, there have been several investigations designed to determine the biological effects of single chemicals or small artificial OBP combinations. However, there is still insufficient information regarding the general biological response to these compounds, and further studies are still needed to evaluate their potential genotoxic effects. In the current study, we evaluated the effect of three drinking water disinfectants on the activity of cytochrome P450 (CYP)-linked metabolizing enzymes and on the generation of oxidative stress in the livers of male and female *Cyprinus carpio* fish (carp). The fish were exposed *in situ* for up 20 days to surface water obtained from the Trasmene lake in Italy. The water was treated with 1–2 mg/L of either sodium hypochlorite (NaClO) or chlorine dioxide (ClO_2) as traditional disinfectants or with a relatively new disinfectant product, peracetic acid (PAA). Micronucleus (MN) frequencies in circulating erythrocytes from the fish were also analysed as a biomarker of genotoxic effect. In the CYP-linked enzyme assays, a significant induction (up to a 57-fold increase in the deethylation of ethoxyresorufin with PAA treatment) and a notable inactivation (up to almost a 90% loss in hydroxylation of *p*-nitrophenol with all disinfectants, and of testosterone 2β-hydroxylation with NaClO) was observed in subcellular liver preparations from exposed fish. Using the electron paramagnetic resonance (EPR) spectroscopy radical-probe technique, we also observed that CYP-modulation was associated with the production of reactive oxygen species (ROS). In addition, we found a significant increase in MN frequency in circulating erythrocytes after 10 days of exposure of fish to water treated with ClO_2, while a non-significant six-fold increase in MN frequency was observed with NaClO, but not with PAA. Our data suggest that the use of ClO_2 and NaClO to disinfect drinking water could generate harmful OBP mixtures that are able to perturb CYP-mediated reactions, generate oxidative stress and induce

Abbreviations: NaClO, sodium hypochlorite; ClO_2, chlorine dioxide; PAA, peracetic acid; CYP, cytochrome P450; MN, micronuclei; OBPs, organochlorine by-products; ROS, reactive oxygen species

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doi:10.1016/j.mrgentox.2006.09.010

genetic damage. These data may provide a mechanistic explanation for epidemiological studies linking consumption of chlorinated drinking water to increased risk of urinary, gastrointestinal and bladder cancers.
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Keywords: Drinking water by-products; *Cyprinus carpio*; Cytochrome p450; Micronucleus; Organochlorine by-products; Cancer; ROS

1. Introduction

Chlorination is the most common means used to disinfect drinking water worldwide. However, while providing protection against pathogenic microorganisms, surface water disinfection may generate highly toxic by-products, such as haloalkanes, haloacetic acids, haloacetonitriles, haloketones and haloaldehydes [1]. These compounds are derived from reactions of chlorine with humic and fulvic acids that are normally found in surface water [2–4]. A number of organochlorine by-products (OBPs) have been shown to be non-genotoxic carcinogens in laboratory animals [5,6]. These compounds are also able to induce mutagenic effects in some biological systems such as bacteria [7], polychaete [8], teleost fish [9,10], mouse cells [11] and human B-lymphoblastoid cells [12]. Long-term studies in rats treated with the disinfectant sodium hypochlorite (NaClO) in drinking water showed an increase in leukaemia in female rats [13]. Several epidemiological studies have suggested a link between consumption of chlorinated drinking water and increased risk of urinary and gastrointestinal tract cancers [14,15]. Studies linking the use of chlorinated water with the development of bladder cancer provide further support for this association [3]. Associations have also been found between consumption of drinking water with high OBP content and adverse reproductive outcomes, such as intrauterine growth retardation, spontaneous abortion and birth defects [16].

In drinking water, OBPs are present as a mixture of chemicals, with a composition that depends on the water source. Both *in vitro* genotoxicity [17] and *in vivo* carcinogenicity testing [18,19] of different artificial mixtures of OBPs showed complex dose-dependent interactions that suggested an overestimation of the overall carcinogenic effect of this group of chemicals. While the current default risk assessment of chemical mixtures assumes that the carcinogenic effect of these chemicals is additive [20], long-term human exposure to OBP mixtures warrants further investigations into both the possible epigenetic and the genetic mechanisms of toxicity of these compounds. Results from these types of studies would help improve risk assessment and would aid efforts aimed at discovering alternative water disinfectants, as replacement for chlorine-containing chemicals, to reduce the risk of adverse health effects. One of the currently proposed alternative disinfectants that has received particular attention over the past few years is peracetic acid (CH_3COO_2H; PAA). This chemical is a potent antimicrobial agent with many applications in hospitals, laboratories and factories [21–23]. Disinfection of drinking water from lakes and rivers with PAA results in the production of carboxylic acids, which are known to be essentially non-mutagenic, with a very low level of genotoxicity in bacterial test systems [24,25].

In this work we evaluated the effects of two OBP-producing disinfectants (NaClO and ClO_2) and PAA in samples of treated lake water on the modulation of cytochrome P450 (CYP)-dependent biotransformation in the livers of *Cyprinus carpio* fish, and on the generation of reactive oxygen species (ROS). These endpoints were studied as possible surrogates for epigenetic mechanisms of carcinogenesis [26–32]. In addition, the DNA damaging potential of the two chlorine-containing disinfectants and PAA was investigated using the micronucleus (MN) assay in circulating erythrocytes of these *C. carpio* fish that were exposed *in situ* (for up to 20 days) to surface waters treated with the three different disinfection protocols. The micronuclei originate from chromosome fragments or whole chromosomes that fail to engage with the mitotic spindle and therefore lag behind when the cell divides. The MN assay in circulating erythrocytes of several species of fish, including *C. carpio*, has been widely used in both *in situ* and *in vivo* exposure to environmental waters (for a comprehensive citation list see Ref. [43]). The relevance of the MN test in such a non-proliferating cell system relies on the MN-PCE test, formerly introduced in the mouse, though in fish erythrocytes the direct derivation of MN-cells from the last proliferating event is not easily ascertainable by staining techniques. The appearance of MN in circulating fish erythrocytes is the ultimate step in their development. MN are generated by segregational errors (due to clastogenic and/or aneugenic events) taking place in the dividing erythropoietic stem cells in the cephalic kidney. According to data from different authors, the estimated time for detection of MN in circulating blood erythrocytes ranges between the second and third week after a clastogenic treatment [9,10], which is compatible

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