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EDITORIAL

Mutagens and carcinogens in drinking water

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Abstract Water is the basic constituent of all living beings; it is, therefore, an essential dietary element and a primary resource. The D. Lgs. 31/2001 is the Italian standard reference concerning drinking-water issues. The purpose of this article is, firstly, to highlight that chlorination, as a water purifying treatment, does not guarantee an absolute absence of risk. On the contrary, it causes the formation of various by-products, many of which are known to be carcinogenic and mutagenic. Secondly, some drinking-water pollutants have mutagenic and carcinogenic properties, giving an appreciable risk for the user. As a result, water reserves, because of their importance to public health, should be properly safeguarded and protected to prevent possible contamination. Although disinfection brings about mutagenic and carcinogenic molecules, we cannot do without it if we want to prevent the much more severe risks due to the presence of pathogens in water used for human consumption.

Keywords Water · Chlorination · Contamination · Mutagens · Carcinogens · Risk

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Introduction

Water is the fundamental constituent of animal organisms; it is the medium through which all metabolic reactions happen [1]. Water is involved in digestive processes, in the regulation of osmotic pressure, in transporting nutrients and in maintaining body temperature. Furthermore, it is well known that some essential elements (selenium, iodine, fluorine) are taken in great amounts through drinking water [2].

When water intake is equal to its output (urine, sweat, respiration and transpiration) the individual is water-balanced [3].

In an adult person water is 60% of the body weight, while at birth it reaches 75%. It is therefore an essential dietary element, whose deficiency produces deleterious effects quicker than food shortage [4]. Water loss equal to 10% of the body weight causes a cessation of physical and intellectual activities [5]. Humans take water through various types of drinks (natural and mineral water, fruit juice, etc.) and as a component of solid foods, in which it is present in various amounts [6, 7].

As a result, water is the medium for all biological processes and a basic and essential dietary constituent. In other words, water is essential for life and, therefore, must be available to all, adequate, safe, accessible [8, 9], wholesome and, above all, should not cause appreciable health hazards, as it is needed for all other types of food [10–13].

Water for human consumption

The D. Lgs. 31/2001 is the Italian reference standard that, by acknowledging the 98/83/EC European Directive, regulates drinking water issues and also defines all analysis criteria and parameters a water sample must undergo in order to be defined "drinkable" [14].

The Decree considers as "water intended for human consumption" all water, whatever its origin, in its original state or after treatment, that is:

- provided to the consumer; or
- used by food industries for the manufacture, processing, preservation or marketing of products or substances intended for human consumption.

In order to be defined as such, water for human consumption should be colourless, tasteless, odourless, free from any particles that constitute a potential danger to human health, must have a chemical composition that is well tolerated by the human body and should not contain any toxic substances (heavy metals, pesticides, etc.) or pathogenic microorganisms.

Water treatments

Disinfection of water for human consumption could be considered the most significant public health measure taken during the last century; destroying pathogens in drinking water has drastically reduced the incidence of waterborne diseases in all industrialised countries [15, 16].

Chlorination is currently the most widely used water treatment due to its action and the low cost of the process [17, 18]. The use of hypochlorite ion (ClO^-) is preferred to chlorination by chlorine dioxide (ClO_2) and chlorine gas (Cl_2); however, it does not guarantee the absolute absence of risks. The addition of those chemicals to water leads to the formation of other compounds, many of which are toxic, as they can cause, among other things, chronic diseases and cancer [19, 20].

The purification process includes the removal of pathogenic microorganisms (Table 1), some minerals (including some heavy metals) and some chemical pollutants (such as nitrogen and organic compounds).

Table 1 Diseases or pathogens that can be transmitted by water

Bacteria	Viruses	Protozoans	Helminths
Cholera	Poliomyelitis	Amoebiasis	Schistosomiasis
Typhoid fever	Hepatitis A and E	Giardiasis	Fascioliasis
Paratyphoid fever	Enterovirus	Cryptosporidiosis	Taeniasis
Salmonellosis	Rotavirus	Toxoplasmosis	
Shigellosis	Adenovirus		
Yersiniosis	Norwalk like virus		
Campylobacter enteritis	Coxsackievirus		
E. coli (EHEC)			
Leptospirosis			

Carcinogenesis and mutagenesis of disinfection/disinfection by-products

Epidemiological studies have been carried out in order to highlight the possible excess of cancer in populations drinking water treated with chlorine. These studies have shown that there is a relationship between drinking water quality and prostate, intestine and anal cancers. Nine percent of all cases of prostate cancers and 15% of anal cancers are attributed to chlorinated drinking-water by-products [21].

Humic and fulvic acids appear to be the main precursors in the formation of the following chlorination by-products: trihalomethanes (THMs), haloacetic acid (HAAS) and haloacetonitriles (HANS), all suspected to be toxic, mutagenic, teratogenic and carcinogenic [22].

These by-products are identified as disinfection/disinfection by-products (D-DBPs, Table 2); the THMs are the most dangerous of these. From a practical point of view, however, the total level of D-DBPs can be significantly reduced by removing or reducing water levels of humic and fulvic acids before chlorination.

It is important to note that the World Health Organization (WHO) has not yet set any standards for HAAS concentrations, while it has put the "MX" 3-chloro-4-dichloromethyl-5-hydroxy-2(5H)-furanone on the list of substances potentially harmful to human health. The "MX" was discovered in 1986 as a disinfection by-product, produced if humic acids are present at the time of chlorination. The MX is often found in water in appreciable concentrations, and because of its mutagenic activity it is dangerous to health. It is estimated that about 30% of the total water mutagenic activity can be attributed to this by-product of disinfection. However,

Table 2 Disinfection/disinfection by-products (D-DBP)

	Health effect
Trihalomethanes	
Chloroform	Carcinogenic, hepatotoxic, nephrotoxic
Trichloromethane	Teratogenic
Dichloromethane	Teratogenic
Tribromomethane chlorine	Teratogenic
Tribromomethane	Teratogenic, nephrotoxic
Acetonitriles	
Chloroacetonitrile	Genotoxic
Dichloroacetonitrile	Mutagenic, genotoxic
Trichloroacetonitrile	Genotoxic
Bromochloroacetonitrile	Mutagenic, genotoxic
Haloacetic acids	
Chlorophenols	
2-Chlorophenol	Foetal toxic effect, carcinogenic
2,4-Dichlorophenol	Foetal toxic effect, carcinogenic
2,4,6-Trichlorophenol	Carcinogenic
Chloroketones	
1,1-Dichloropropane	Mutagenic
1,1,1-Trichloropropane	Mutagenic

due to a lack of complete toxicological data, there is no reference guide for the dissolved MX [23]. Disinfection by ClO_2 is increasingly used rather than ClO^-, because it does not produce toxic THMs, the chlorite ion being its by-product. However, there are studies that have confirmed chlorites' potential mutagenicity and genotoxicity. The EU directive does not includes chlorites as undesirable, while the Italian norm, inspired by the precautionary principle, considers 200 g/l the acceptable threshold [14]. This value was taken from the WHO Provisional Guideline Value [24, 25], although the latter is just a "guide" and "provisional".

Possible drinking-water pollutants with high carcinogenic and mutagenic activity

The risk of mutagenicity and carcinogenicity associated with drinking water may also arise from potential contamination by natural or man-made pollutants such as: nitrates, polycyclic aromatic hydrocarbons (PAHs), heavy metals (e.g., arsenic, As; lead, Pb; mercury, Hg) and pesticides; their acceptable thresholds are established by the D. Lgs. 31/2001. However, in addition to the issues related to possible man-made drinking-water contamination, it must be noted that very often the water that is supposed to be used for human consumption is not suitable for the purpose because, due to anomalous but entirely natural geochemical conditions, it does not meet the safety standards imposed by current regulations.

Nitrate

The Environmental Pollution Agency (EPA-USA) has established a maximum contaminant level (MCL) of 10 mg/l (as nitrogen) [26] for nitrates in drinking water. Nitrates are not very toxic in themselves, but they are teratogenic; however, nitrites, which originate from them through the action of enzymes present in the human body, are much more toxic. For similar reactions, carcinogenic N-nitroso compounds, suspected of high carcinogenic potential [27, 28], are formed from nitrites. An excessive nitrate blood level can lead to insufficient transport of oxygen in the bloodstream. The most well known and documented health hazard associated with high levels of nitrate in drinking water is methaemoglobinaemia or blue-baby syndrome. As a consequence, in some Eastern European areas, where water in its origin is contaminated with nitrate levels as high as 50–100 mg/l, pregnant women and children under 1 year should take only bottled mineral water. Other important potential effects associated with high levels of nitrates are the risk of stomach cancer and malformations at birth [27–29]. At the moment, epidemiological evidence to show an association between nitrate intake and cancer is not considered sufficient, and thus the current WHO guideline for nitrate in drinking water is established only to prevent methaemoglobinaemia [30]. It should be mentioned that it has recently been shown that chlorination, up to a certain extent, controls nitrates (depending on their concentration), thus lowering their risk to human health.

Polycyclic aromatic hydrocarbons (PAHs)

An Italian study has shown that, for humans, food is the most important source of exposure to PAHs, in that the daily intake of carcinogenic PAHs is 1–4 μg. The inhalation exposure is of secondary significance. The most commonly blamed foods are those that undergo cooking, processing or storage such as being smoked, grilled and roasted [31].

PAHs in drinking water generally come from coatings, tar or bitumen, or the water distribution pipelines themselves [25].

PAHs as such are not carcinogens, but in the process of making them water soluble, the human body brings about some carcinogenic by-products. Once ingested, PAHs are rapidly absorbed through the gastro-intestinal tract and distributed in various tissues, including the foetus. The mechanism by which these compounds act as carcinogens is still unclear and several theories have been formulated. The best known is the "bay region" of Pullman and Pullman [32].

For individual PAHs and for their complex mixtures, the evaluation of carcinogenicity as well as of genotoxicity overlap; that is why their damage to DNA, induction of mutations and long-term carcinogenic effects are evaluated together [33, 34].

The International Agency for Research on Cancer (IARC) has included benzo(a)pyrene (BaP) and other PAHs in Classes 2A and 2B (possible or probable carcinogens to humans) because of mutagenic effects demonstrated in studies conducted *in vitro*; for them it is assumed that there is no minimum threshold dose.

Heavy metals (As, Pb, Hg)

Many heavy metals belong to the so-called "trace elements", but in recent decades the flow from the hydrosphere to man for several heavy metals such as As, Pb and Hg has increased abundantly due to seasonal inputs by using pesticides, or to natural release from the soil into ground waters [35]. A significant increase of the intake of those elements through drinking water has already been reported and this will certainly be worse in the future. It should be noted that As, Pb and Hg have been associated with various forms of cancer [36].

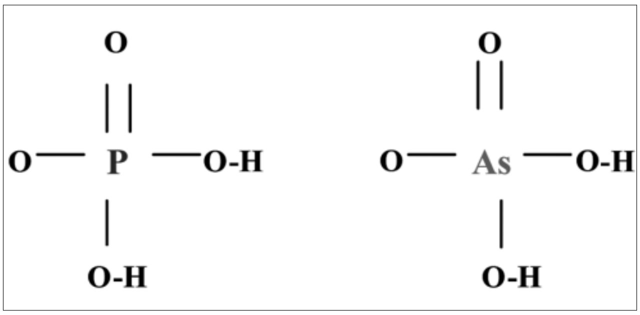

Fig. 1 Comparison of phosphate and arsenate structure

Although As is widely distributed, and its daily intake, even in the absence of pollution, can reach 0.5 mg, its presence in food or beverages raises many concerns. Its toxicity depends on its chemical structure, in that the inorganic are more toxic than the organic compounds [37].

Arsenic acid interacts with the cellular metabolism by inhibiting the formation of ATP; it can also replace the phosphoric ion in phosphate sugars. The arsenate may in fact mimic the endogenous phosphate so well that it may be included in its metabolic pathway until it becomes toxic; for this reason its toxicity has been explained in terms of "molecular mimicry" (Fig. 1) [38].

Arsine acid, in contrast, forms stable bonds with skin and kidney enzyme reactive groups, modifying them. As a matter of fact, As is associated with skin cancer [39]. The arsenites also accumulate in leukocytes and depress the activity of enzymes containing thiol groups, including the DNA polymerase, resulting in a mutagenic effect. As is also often included in the composition of some pesticides that contaminate ground- as well as surface water. A large epidemiological study proved that ingestion of arsenic through drinking water or long contact with arsenic as a pesticide predisposes to skin or lung cancer [40]. Arsenic, unfortunately, is present in almost all drinking water, and those that are described as "chronic endemic regional hydro-arsenicosis" are attributed to the use of naturally contaminated domestic water.

Pb intake may occur through food (65%), water (20%) and air (15%). Pb is more likely to contaminate drinking water through pipe corrosion when the water is slightly acidic; that is why it is required that public drinking water systems are periodically checked for pH.

Pb is also a component of many pesticides and can cause numerous side effects such as anaemia, hypertension, nephro-toxicity, etc.

The Pb ingested by a pregnant woman through drinking water can cross the placenta and be deposited in the foetus' brain, causing mutagenic and teratogenic effects (abnormal brain development) as well as abortion. A link has been proven between lead ingested with drinking water and mental and physical child growth retardation [36].

Hg contamination is a worldwide problem too. The use of this metal was banned after it was proven that methyl-mercury (CH_3Hg) is much more toxic than Hg inorganic compounds; it is formed by bacteria in anoxic areas and it caused the 1960s Minamata Bay disaster. Hg aerial emissions have been banned too, since they can be converted into CH_3Hg and enter the drinking water system. This decision was taken following a federal agencies (EPA, FAO and WHO) study proving that foetuses can be seriously harmed if their mothers drink this type of water. CH_3Hg also crosses the placenta to the foetus, thus producing a mutagenic and teratogenic effect, usually highlighted by a statistically significant reduction of the cerebellum weight. Exposure during pregnancy, even at low doses, can cause significant neuro-functional deficits in the newborn [41].

CH_3Hg can also cause kidney cancer; it is, therefore, considered a potential carcinogen for humans [42].

Pesticides

The term "pesticides" defines a class of chemical compounds used in agriculture to fight pests and other organisms harmful to humans, animals and plants. These compounds vary widely in their chemical compositions, ranging from plant extracts such as pyrethrum, to mineral salts and oils, up to very sophisticated organic compounds. Heavy pesticides are substances that persist in the environment for long periods of time. By their very nature, pesticides can be hazardous to humans, since their purpose is to kill or harm living organisms [43]. Pesticides can be absorbed by inhalation, skin contact or through the digestive system. Among the pesticides, chloride and phosphoric insecticides are the most toxic (Table 3). Environmental and food pollution is mainly due to chlorinated insecticides [44, 45].

A study by the Ministry of Health (Pesticides Residues National Plan, run in Italy in 2005) evaluated Italians' exposure to the 148 most commonly used pesti-

Table 3 Examples of pesticides found in the environment

Chemical group	Examples	Toxic effects
Organochlorines	DDT, lindane, dieldrin, chlordane	Carcinogenic, hormonal agonist, neurotoxic
Organophosphates	Parathion, chlorpyrifos	Neurotoxic, dermatotoxic
Carbamates	Malathion, aldicarb, Baygon	Neurotoxic, dermatotoxic
Pyrethroids	Cyfluthrin, permethrin, fenvalerate	Neurotoxic, hormonal agonist, immunotoxic
Herbicides		
Dipyridyl	Paraquat, diquat	Pulmonary fibrosis
Other	Atrazine, alachlor	Carcinogenic

cides present as residues in food. The study showed that none of the average amount of the 148 pesticides under review was above the acceptable daily dose. This is undoubtedly comforting if we do not consider the effects of the combination of several pesticides in the same product, which is still an open public health issue.

Surface water that is to undergo disinfection for human consumption, being less protected than underground water, is usually checked for pesticides [46]. The Lyon IARC [47], after a study on pesticides, concluded that some of them may cause stomach, pancreas, colon, bladder, kidney and skin cancer, as well as lymphomas.

The evaluation of the presence of pesticide residues in water and their effects on humans and on other exposed organisms is complicated by a number of problems. One of these is the phenomenon of seasonality in surface waters, with a trend in the levels of concentration that is affected by the cultivation periods and by weather conditions. Another is the existence of mixtures of substances, with the possibility that their synergistic toxic effects are higher than that of the individual substances [45].

Conclusions

Drinking-water reserves, because of their importance to public health, are a collective concern. It is everybody's duty to ensure that they are properly safeguarded and protected. The legislator, the controller and even each individual user all have a role to play in terms of properly using water as well as appropriate planning of solid waste disposal, and civil and industrial sewage drainage, in order to avoid possible water contamination. The resulting approach should be an effective integration of all named operational plans.

The direct and immediate risk to health and life caused by the presence in water of pathogenic microorganisms makes it unthinkable to abandon the process of disinfection; as a result, the parameters proposed for the by-products of disinfection should not be so restrictive as to impair its use. Water disinfection has, in fact, allowed people to have wholesome water and to prevent many diseases.

Avoiding disinfection, however, should be strongly recommended, when possible, as it increases the quality of water and eliminates the risks associated with disinfection.

Nevertheless, some important issues are still being debated, including the identification and understanding of the risks arising from low levels of environmental chronic exposure, as well as from complex compounds.

It is advisable that these topics should be the primary goals of future scientific research.

Conflict of interest The authors declare that they have no conflict of interest related to the publication of this manuscript.

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