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MUTAGENS AND CARCINOGENS IN WATER RESOURCES

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WATER RESOURCE PLANNING, DEVELOPMENT AND MANAGEMENT

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PREFACE

Water is the basic constituent of all living beings; it is, therefore, an essential dietary element and a primary resource. Water resources, because of their importance to public health, must be properly safeguarded and protected to prevent possible contamination. The International standard references concerning water resources are various and, though they are based on WHO guidelines, they are extremely diversified in relation to local issues and emerging problems. The purpose of this chapter is to highlight that natural or antropic environmental contamination and water treatments, like drinking water treatments, may pose health at risk. As a matter of fact, many carcinogenic and mutagenic substances are released in natural or treated water giving an appreciable risk for the user. The major mutagenic and carcinogenic molecules that can result from environmental contamination are thus described, as well as those, known and emerging, produced by the processes of water purification. 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; therefore, it is necessary to know well the molecules that are formed during the processes of drinking water in order to properly set the necessary treatments for their removal from water resources.

INTRODUCTION

There is no life without water. It is present in large quantities (from 65% to 95%) in all living forms, both plants and animals. In addition to its many physiological and metabolic functions in the living world, water is important for human health as well as an energy source, as raw material in technological processes and it is a support for recreational and sport activities [1; 2; 3].

Water is essential to humans as food and drink.

Prior to the industrial revolution, water did not suffer much change as it was used for the basic needs of man, while with the advent of the industrial age man has changed the use of water and has seriously violating its natural characteristics, introducing into it a multitude of chemicals and organic substances making it potentially dangerous for human health.

The expansion of urbanization, in fact, has led to a growing demand for water and to an increment of the production of municipal and industrial wastewaters. The final recipient of wastewater has often been the very same water reservoir, unable of self-purification due to massive and frequent spillage of effluents [4].

The water reservoir (river, lake, ocean etc…) is a complex system, being a place of exchange between water, sediment, soil and air.

For this reason the water resource more than water itself has become one of the most important determinants of health.

The Council of Europe in 1968 adopted the European Charter on Water, that still today represents a fundamental document for the protection and management of water resources, highlighting the criticality related to their management.

In 2001 the associations of the main experts in water issues (precisely the American Water Works Association, The European Union Association of Water Operators and The Australian Water Services Association) set as a target for the XXIst century to provide drinking water that should be safe from the sanitation point of view and that should inspire consumers' confidence[3].

Chapter 1

WATER SOURCES AND THEIR AVAILABILITY

Water resources are classified in fresh and salty waters. Our planet is covered for 71% by water; however 97% of it is salty and only 3% is fresh; about 69% of this is in the form of snow and ice in the Arctic and Antarctic areas.

Depending on their source, natural waters are classified as:

- rainwater (rain, snow, hail, dew, frost);
- groundwater (deep aquifers or groundwater);
- surface water (seas, rivers, lakes, springs).

Groundwater is mineral water fed by the infiltration of rainwater through the soil that acts as filter for suspended matter.

Sometimes groundwater spontaneously resurfaces, thus becoming spring water.

Deep groundwater may remain undisturbed by anthropogenic effects for thousands years. However, most groundwater is not very deep and therefore gets into the hydrological cycle.

Surface waters have highly variable composition depending on the geographical and environmental conditions.

Water resources are used in various ways including direct consumption, agricultural irrigation, fisheries, hydropower, industrial production, recreation, navigation, environmental protection, sewage disposal and treatment, and for industrial effluents.

Water resources refer to groundwater and surface water in a given area.

Water is made available by the natural water cycle of the atmospheric-oceanic-terrestrial system. In most forms, water is a renewable resource; however, not all natural waters are renewable and renewable waters can become non-renewable by human actions such as industrial and agriculture contamination.

The fresh water used by humans in the form of deep water or groundwater and surface water (rivers and lakes) is unfortunately just 0.01% of all water resources [5].

Even today water is used without regard to its decline as a resource; although it is not yet evident to the ordinary consumer, nevertheless the trend towards reduction in availability is already plotted.

Water stress shows a commensurate ecological stress [3; 6].

WHO has determined that access to water is a need and a fundamental human right [7; 8].

Still today, contaminated water is the second most important cause of infant death (<5 years).

It is known that in the nineteenth century Chicago was the city of typhus, having about 20,000 cases per year; reason being that the city had water drawn from Lake Michigan that was also the catchment area of municipal wastewater [3].

1.1. Contamination Sources of Water Resources

Water pollution is caused from the direct or indirect human introduction of substances into the water environment such as to harm living resources, affect human health and impair water environment quality.

Water resources pollution can also be of natural origin (see Table 1).

It is important, however, to say that water resources affected by pollution of natural type (eruptions, floods, degradation of dead plants or animals, etc ...) often restore their natural conditions following self-purification.

Anthropogenic pollution originates from industrial, agricultural, animal husbandry and urban activities.

Agriculture is world-wide recognised as being the leading contributor to on point source pollution of water resources.

Nutrients from fertilizers (e.g. phosphorus and nitrogen), in fact, cause eutrophication while pesticides have been shown to cause toxicity in humans, crops, livestock and wildlife .

In 1999, the USEPA has indicated eutrophication as the most critical factor impairing surface water quality in the United States, and agriculture is considered the most important source of nutrients for water resources.

In South Africa, already 30 years ago, eutrophication was recognised as a priority water resource management problem, and this problem is still today unresolved [9].

Among contaminants there are organic (pesticides, plasticizers, detergents, hydrocarbons etc...) and inorganic chemicals (metals and heavy metals, ions ecc..).

The potential harm for human health of organic pollutants in drinking water is widely focused on worldwide. Pollutants released into water may have potential mutagenic, teratogenic and carcinogenic effects on human health; also genotoxic pollutants are more and more released into the aquatic environment [10].

The mutagenic and carcinogenic effects, however, are not just due to the use of potentially polluted water resources, but also to the use of disinfected water.

Some risks have been associated with chronic exposure to disinfected water due to disinfection by-products released during chlorination and ozonization processes [11].

Typically, the ordinary citizen or user links water to microbial diseases because he knows more about it, due to a more effective risk communication and therefore a more correct risk perception; instead, he knows very little about the risk of degenerative chronic diseases due to exposure to drinking water or contaminated water.

For these reasons, legislators had to define with certainty the pollutants levels considered dangerous or unacceptable and therefore not to be exceeded.

Although the guidelines are all drawn from the WHO document [7], laws relating to drinking water and to management of water resources show a differentiation among the various Countries due to specific territorial and geographical issues.

Table 1. Some water contaminants and their human health effects

Contaminants	Human Health Effect
Protozoa, Bacteria, Virus, Helminthes	Contagious deseases
Heavy metals (Pb, Hg, Cd, As, Cr, Ni, V) Nitrates and nitrites	Toxic and carcinogenic effects Methaemoglobinaemia (blue-baby syndrome) and carcinogenic effect.
Organic halogenic solvents	Toxic and carcinogenic effects
Chloride and phosphoric pesticides	Toxic and carcinogenic effects
Hydrocarbons	Toxic and carcinogenic effects
Radioactive substances (U,Rn)	Carcinogenic effects
Disinfection by-products of chlorine disinfection (Perchlorates, THMs, MX or MX compounds HAAs, HANs, ecc..)	Genotoxic, mutagenic and carcinogenic effects
Disinfection by-products of ozone disinfection (Bromate, Chlorite and Chlorate, MX, MX compounds, Aldheydes)	Genotoxic, mutagenic and carcinogenic effects
Disinfection by-products of UV disinfection (free radicals)	Genotoxic, mutagenic and carcinogenic effects

1.2. Guidelines of Waters Management

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 that a water sample must undergo in order to be defined “drinkable”.

The D. Lgs.152/2006 instead, in Part III, sets down the rules for soil conservation and combating desertification, and the norms for the protection of waters against pollution and for the proper management of water resources.

The 1996 NHMRC Australian Drinking Water Guidelines defines the criteria for acceptability of drinking water for Australia and New Zealand. In the United States there is a USEPA directive. WHO provides values that are considered to be “safe” for a number of substances in the Guidelines for Drinking Water Quality.

It is important to note that the various laws (including WHO guidelines) concerning drinking-water differ not only on the basis of limits adopted but also for the diversification of the contaminants subject to limits, such as perchlorate, which is a problem for U.S. and Canadian waters while it is not looked for in Europe and Australia.

With the drafting of the D. Lgs. 152/2006 and the 2000/60/EC Water Framework Directive the legislative framework for the policies of protection and sustainable use of water resources was heavily modified.

To this end, in Italy the principle that "polluter pays" has been already introduced by the 36/94 Law.

Moreover with Review of Annex X to Directive 2000/60/EC list of 33 main hazardous substances in water has been added.

Chapter 2

MUTAGENIC AND CARCINOGENIC CONTAMINANTS IN WATER RESOURCES

Organic pollutants made up of hydrogen, carbon and oxygen, are petroleum products (e.g. gasoline, oil, pesticides), solvents, cleansing agents, polychlorinated biphenyls, human and animal wastes. Many of these pollutants are mutagenic and carcinogenic to humans and animals, and many of them are also persistent and bioaccumulative.

Among the environmental pollutants, however, even the inorganic substances are of significant importance.

Possible pollutants, mutagens and carcinogens, most commonly involved are pesticides, some heavy metals, nitrates, polycyclic aromatic hydrocarbons (PAHs), all regulated by the Italian D. Lgs. 31/2001 and also by the guidelines of some Countries [2].

Other contaminants, such as perchlorate, MTBE, or MX indicate specific local problems of industrial and geographic origin.

2.1. THE PESTICIDES

Pesticides are a class of chemical compounds used in agriculture to fight pests and other organisms harmful to humans, animals and plants.

These compounds vary in their chemical compositions, ranging from plant extracts (pyrethrum) up to very heterogeneous organic compounds.

Pesticides can be absorbed by inhalation, skin contact or through the digestive system.

After many studies on pesticides, the IARC (International Agency for Research on Cancer) of Lyon concluded that some of them may cause stomach, pancreas, colon, bladder, kidney and skin cancer, as well as lymphomas.

Exposure to pesticides increases risk of cancer for farmers but also for water consumers.

We have identified more or less 400 different active ingredients in the world, and the pesticides at present are object of monitoring analysis of water for human consumption and in general of water resource. Surface waters are being less protected than underground water from pesticides pollution [2].

The Environmental Working Group in Washington has calculated that every day in the U.S. one million under-five children ingest an overdose of organophosphorus pesticides; it is important to emphasize that children are more at risk than adults, as their cell proliferation is greater, their immune system is immature and their ability to react to pollutants is reduced.

Tumors in children are due to direct exposure to environmental pollutants but also to exposure of the mother during pregnancy.

This was confirmed by the Setil study (Epidemiological study on childhood cancers in Italy).

Current international legislation on pesticides sets limits without taking any account of the age variable, thus the WHO standards protect only adults, not children and babies.

When one adds that those limits do not take into account the exposure to combination of several pesticides the situation worsens for adults but for children becomes dramatic.

Pesticides are also responsible for male infertility; dibromo-3-chloropropane or dibromochloropropane (DBCP), used in the eighties, has made sterile males who worked in the orchards in California [12].

The effects of the combination of several pesticides in the same product (including water) is still an open public health issue arising from the possibility that their synergistic toxic effects are higher than that of each individual substance.

2.2. PAHS

PAHs are aromatic hydrocarbons, with two or more fused benzene rings, of natural as well as anthropogenic origin.

PAHs are toxic and can cause mutagenicity, therefore several of them have been classified as probable or possible carcinogenic by the International Agency for Research on Cancer [13].

PAHs occur in oil, coal, and tar deposits, and are produced as byproducts of fuels burning.

PAHs adsorbed by particulate matter are thrown to the ground by rain, and through the "leaching" process reach rivers, lakes, lagoons and coastal areas.

PAHs in drinking water generally come from coatings, tar or bitumen, of the water distribution pipelines themselves, while water resources are polluted by PAHs from unburned oil spilled into surface and marine waters or by release of fuel burning by-products [6].

Once ingested, PAHs are rapidly absorbed through the gastro-intestinal tract and distributed to various tissues, including the foetus.

PAHs as such are not carcinogens, but in the process of making them water soluble, the human body brings about some carcinogenic by-products (see Table 2).

The mechanism by which these compounds act as carcinogens is still unclear but it was noted that PAHs are modified in the cells into epoxide K-region that bind to DNA thus expressing their mutagenicity and consequently their carcinogenicity, for which there is no threshold dose [2].

PAHs may be associated with specific breast tumor p53 mutation subgroups rather than with overall p53 mutations and may also be related to breast cancer through mechanisms other than p53 mutation [14].

2.3. HEAVY METALS

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 Arsenic (As), Lead (Pb), Mercury (Hg), Chromium (Cr), Nickel (Ni), Cadmium (Cd), has increased abundantly due to release from industrial processes, to using pesticides or to natural release of

Uranium (U), Radon (Rn), Vanadium (V) and more from soil into groundwater.

Toxic metals represent the ultimate form of persistent environmental pollutants because they are chemically and biologically indestructible.

Carcinogenic metals are typically weak mutagens and with the exception of chromium, they do not form DNA adducts which represent a key initiating event in the cancer-inducing activity of organic carcinogens [15].

Table 2. Target organs of carcinogenicity of single PAHs for various exposure route

SINGLE PAHs	EXPOSURE ROUTE			ORGANS TARGET
	Skin	Oral	Air	
Benzo(a)pyrene	x	x		Breast, lung, liver
‘‘		x		Stomach
Benzo(a)anthracene	x	x		Lung, liver
Benzo(b)phenanthrene	x			Skin
Benzo(j) phenanthrene	x			Skin, lymphatic tissue
‘‘			X	Lung
Benzo(k)fluoranthrene	x			Skin, endometric
‘‘				Skin
‘‘			X	Lung
Benzo(g,h,i)perylene	x		X	Skin, lung
Chrysene	x			Skin
‘‘		x		Fegato, lung, lymphatic tissue.
Dibenzo(a,c),(a,j),(a,h) anthracene	x			Skin, lung
‘‘		x		Stomach
Pyrene	x			Skin

2.3.1. Arsenic

Particular attention has been given by the legislature to Arsenic (As), that is very dangerous to human health because of its chemical form.

The arsenic acid interacts with the cellular metabolism by inhibiting the formation of ATP and because it can replace the phosphoric ion in phosphoglucides, as it has the characteristic "molecular mimicry" of phosphorus.

Arsine acid forms stable bonds with skin and kidney enzyme reactive groups, denaturing them, thus being more toxic than arsenic acid.

As is often included in the composition of some pesticides. It causes mutagenic effects and it is associated with skin, lung and bladder cancer [2; 15].

The threshold of As in drinking water recommended by WHO and the European Union is 0.01 mg/l.

Epidemiological evidence indicates that As concentration exceeding 50 mg/l in drinking water is harmful to public health; nonetheless, many developing Countries are still having a threshold of 50 mg/l.

It has been generally accepted that environmental contamination by As is causing a significant and global health problem.

Arsenicosis is frequent in some areas of India, Bangladesh, PR China, Taiwan, Vietnam and Nepal. For these endemic areas, the major arsenic exposure pathway is believed to be from drinking contaminated groundwater [16; 17].

2.3.2. Chromium

Chromium (Cr) is a naturally-occurring element found in rocks, animals, plants and soil. It is widely used for industrial processes.

The three main forms of Cr are Cr(0), Cr(III), Cr(VI). Cr(III) is relatively non-toxic but it is an essential trace element in human diet, whereas Cr(VI) is very toxic, mutagen and a potential carcinogen.

Exposure to Cr (except for occupational exposure) occurs from ingesting contaminated food or contaminated drinking water.

In the USA limits are set for Cr in discharges: 170 mg/l of Cr (III) and 0.050 mg/l of Cr(VI), while the USEPA Drinking Water regulation limits the total Cr in drinking water to ≤ 0.1 mg/l.

Contamination of groundwater by Cr in numerous localities primarily results from uncontrolled or accidental release into the subsurface environment of Cr-bearing solutions, used in various industrial applications, [18; 19].

One example of widespread exposure is the presence of significant contamination with Cr(VI) in approximately 30% of the drinking water sources in California [15].

Numerous studies have evaluated the genotoxicity of Cr(VI) compounds and provided evidence of Cr(VI)-induced DNA strand breaks, chromosome aberrations, increased sister chromatid exchange, unscheduled DNA synthesis, and DNA-protein crosslinks [20; 19].

Small Cr-DNA adducts are the most abundant form of Cr(VI)-induced genetic lesions in mammalian cells, and they are responsible for all mutagenic damage generated during Cr(VI) reduction with cysteine and ascorbate.

Exposure to Cr(VI) is known to induce in human cells a series of gross chromosomal alterations, particularly telomerase-negative in primary cells [15].

Environmental exposure of humans to Cr(VI) through drinking water is particularly correlated with stomach cancer.

The greater toxicity of Cr(VI) compared to Cr(III) is related to two factors:

- the higher redox potential of Cr(VI) [21];
- the greater ability of chromium(VI) to enter cells [22].

Cr(VI) is shown to be involved in Fenton-like oxidative cycling, generating oxygen radical species [23] and the formation of those radicals responsible for many of the deleterious effects of Cr on cells, including lipid peroxidation [24].

The IARC and the National Toxicology Program (11th Report on Carcinogens) have determined that Cr(VI) is a carcinogenic compound for humans.

The FDA has established that the chromium concentration in bottled drinking water should not exceed 1 mg/l.

2.3.3. Mercury

Mercury (Hg) is a metal whose origin in the environment is both, natural and anthropogenic (see Table 3); however, this partition is only theoretical, since it is very difficult to precisely quantify the natural contributions in the overall amount.

The largest release of Hg results from natural erosion of the earth crust and from volcanic activity.

Effluents from industries are potentially the most hazardous, thus in recent decades it has been tried to reduce contamination allowing only closed-loop processing.

In the marine environment mercury undergoes transformation by micro-organisms into organic compounds such as methylmercury (CH_3Hg).

Hg contamination is a worldwide problem [2].

There are three main categories of mercury:

- elemental Hg,
- inorganic Hg compounds,
- organic Hg compounds (CH_3Hg).

With the industrial revolution, anthropogenic sources have significantly contributed to the release of Hg into the environment

Table 3. Hg Releases (% tot) in European countries

Country	Direct Water Releases	Indirect Water Releases
Holland	0,6	3,9
Portugal	0,6	-
Greece	1,2	
Sweden	2,8	0,7
Finland	3,3	-
Austria	5,0	-
Germany	5,3	19,3
Belgio	5,9	1,2
United Kindom	10,6	-
Spain	14,1	32,1
France	17,3	18,6
Italy	33,2	15,7
Ireland	-	-
Denmark	-	-
Luxemburg	-	-
EUROPE	-	-

Though in recent decades the industrial use of Hg has been reduced significantly, it is still used in industrial sites; in agriculture, instead, it has been absolutely prohibited [25].

From 1570 until 1900, in Central and South America a procedure involving the use of amalgam of mercury with the detritus of mining was used to extract silver and gold; for every ounce of silver produced about one gram of Hg was released into the environment.

Today this practice continues to be implemented on a large scale in Brazil for the gold mining and this causes significant air and water pollution of the Amazon river [26].

CH_3Hg is a highly toxic substance with a significant number of adverse health effects, including neurotoxicity and genotoxicity.

WHO classifies CH_3Hg as a possible carcinogen.

Exposure to CH_3Hg during pregnancy, even at not teratogenic doses, may cause significant neurofunctional deficits in the newborn [27; 28].

Experimental studies performed on mice exposed to high doses of CH_3Hg showed the occurrence of kidney tumors; in rats, exposure to the substance produced ultrastructural changes and degeneration of renal tubules; in males, it seems to be able to block spermatogenesis [27; 29; 30].

2.3.4. Lead

Seawater contains trace amounts of lead (Pb) (2-30 ppt); rivers, instead, contain an average of 3 to 30 ppb.

Exposure to Pb causes a variety of health problems mainly in women and children.

Pb intake may occur through food (65%), water (20%) and air (15%).

Water is rarely an important source of Pb exposure except where Pb is a constituent of the pipes. In that case Pb is released in 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.

Recently, the problem again received particular attention in the United States [31]. In Europe several Countries (e.g. the United

Kingdom, Austria and Germany) are known to have significant numbers of buildings with elevated concentrations of Pb in tap water [32; 33].

In Australia, instead, little is known about drinking water as a source of Pb poisoning, probably because, unlike Europe and the USA, in Australian homes Pb pipe plumbing is not widespread.

Removal of old pipes is costly but it is the most effective measure to reduce Pb exposure through water [7].

The maximum acceptable level of Pb (and other heavy metals) in drinking water has been established by the NHMRC in the "Australian Drinking Water Guidelines" at 0.01 mg/L (lowered from 0.05 mg/L). The use of Pb based solder on drinking water pipes has been banned in Australia since 1989.

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

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 as well as abortion.

A link has also been proven between Pb ingested with drinking water and mental and physical child growth retardation [2].

WHO had fixed for Pb a limit of 50 ppb in 1995, which has been decreased to 10 ppb in 2010.

2.3.5. Nickel

Nickel (Ni) combined with other elements occurs naturally in the earth crust and it is the 24th most abundant element.

It is found in all soils, and it is also emitted from volcanoes. Ni can also be released in industrial waste water.

Under acidic conditions, Ni is more mobile in soil and might seep into groundwater.

The exposure to Ni can occur by air, drinking water, tobacco smoking, but also by skin contact with soil, bath or shower water, or metals containing Ni.

In water and wastewater, Ni can exist either dissolved or attached to suspended material. The concentration of Ni in river and lake water is very low, with average concentration usually less than 10 ppb.

The average concentration of Ni in drinking water in the United States is between 2 and 4.3 ppb.

The U.S. Department of Health and Human Services (DHHS) has determined that Ni compounds are known as human carcinogens.

IARC and USEPA have determined that some Ni compounds are carcinogenic and that metallic Ni may possibly be carcinogenic to humans.

These conclusions were based on studies on workers exposed to nickel and on laboratory animals [34].

Although there is no evidence that soluble Ni acts as a complete carcinogen in animals, nevertheless there is limited evidence suggesting that it may act as a tumor promoter because it is able of causing genotoxic effects in vivo to nuclear sites of target cells [35].

2.3.6. Cadmium

Cadmium (Cd) is found in the earth crust at a concentration of 0.1–0.5 ppm.

The Cd concentration in natural surface water and groundwater is usually <1 μg/l. It is also a natural constituent of ocean water with average levels between less than 5 and 110 ng/l, while the concentrations of Cd in polluted waters in the USA have ranged from <1.0 to 77 μg/l.

Natural emissions of Cd into the environment can result from volcanic eruptions, forest fires, generation of sea salt aerosols.

In surface water and groundwater, Cd can exist as hydrated ion or as ionic complex with other inorganic or organic substances.

Manufacturing and application of phosphate fertilizers, fossil fuel combustion, and waste incineration and disposal are the main anthropogenic sources of Cd in the environment.

For the U.S. population, exposure to Cd through drinking water supply is of minor concern. Cd, in fact, can accumulate from polluted soil and water in plants and organisms, thus entering the food chain.

Some initial studies in European workers exposed to Cd indicated an elevation in prostate cancer; however, results were not statistically significant.

Strong evidence that Cd inhalation can cause lung cancer exists only in studies on rats.

Among the mechanisms involved in Cd carcinogenesis, the DNA repair inhibition is the predominant [36].

The DHHS decided that there were sufficient human and animal data to conclude that Cd is a known human carcinogen; likewise, IARC classified Cd as carcinogenic to humans (Group 1).

The EPA has classified Cd as a probable human carcinogen by inhalation (Group B1) based on its assessment of limited evidence of an increase in lung cancer in humans and sufficient evidence of lung cancer in rats [37].

2.3.7. Vanadium

Vanadium (V) is naturally present in soil, water, and air. It is widely distributed in the earth crust at an average concentration of approximately 100 mg/kg.

V is present as:

- V metal
- V pentoxide
- Vanadyl sulfate and sodium metavanadate

Natural sources of V include dust, marine aerosol, and volcanic emissions, but V is released also as industrial pollutant by oil refineries and power plants using V rich fuel oil and coal.

The partitioning of V in water and soil is influenced by many factors including water and soil acidity and the presence of particulate.

V concentrations in surface water can range from 0.04 to 220 μg/l depending on the area [38].

Only 3-20% of V is absorbed from the digestive tract and we know nothing on its absorption through the skin.

The average concentration of V in tap water is approximately 0.001 mg/l, with a daily intake in adults of approximately 0.002 mg/die.

No studies have verified the carcinogenic potential of V in humans. Lung cancer has been found in mice exposed to V pentoxide and the IARC, based on this evidence, has determined that V is a possible carcinogen for humans.

In the same way, no studies have verified effects of V on the reproductive system in humans after oral exposure, though decreased sperm count and motility have been observed in exposed rats.

The results from oral exposure were negative for carcinogenicity; however, they were inadequate for evaluating carcinogenic effects because insufficient numbers of animals were used, a complete histological examination was not performed, and only one exposure dose per study was evaluated.

As a conclusion, at present there are no reliable data about V carcinogenicity [39].

2.4. RADIOACTIVE SUBSTANCES

2.4.1. Uranium

Uranium (U) is a natural metallic radionuclide; it is present in water, air and food supplies through leaching from natural deposits in soil, emission of nuclear industries, coal or fuel combustion and dissolution of phosphate fertilizer.

U exhibits a chemical toxicity and a reproductive toxicity (see Table 4) which can, in the case of chronic exposure, lead to nephrotoxicity. Furthermore, due to its radioactive decay, U can also cause cancers [40] (see Table 5).

Through drinking water U increases calcium and phosphate urinary excretion.

The mean content of U in Italian mineral water ranges from 4 to 7.22 mg/l [41].

Provisional threshold of U proposed by WHO and USEPA is 15 mg/l and 30 mg/l respectively In nature, U is found as ^{238}U (99.284%), ^{235}U (0.711%) and ^{234}U (0.0058%).

U decays slowly by emitting an alpha particle.

The exposure to U and its decay products, especially Radon (Rn), is widely known as health threat.

Humans can be exposed to U or/and to Rn by inhaling air particulate matter or by ingesting contaminated water and food.

Most of the ingested U is excreted during digestion. U tends to bioaccumulate and stay for many years in bone tissue due to its affinity with phosphates.

A recent risk assessment review of carcinogenicity caused by exposure to hazardous chemicals, including radiation, has been questioning the assumption that there is no need for establishing a threshold. In fact, with specific reference to radiation, there is an increasing biological evidence that there is a threshold for radiation-induced carcinogenicity.

The US National Academy of Sciences has determined that some cancers (bone sarcomas and carcinomas of the head sinuses) are due to oral exposure to U; however, their report noted that this cancer has not been observed experimentally in exposed humans therefore they concluded that exposure to natural U may have no measurable effect; conversely the IARC has no classification for U [42].

Table 4. Genotoxicity of U in vitro° and in vivo*

Species	End point	Exposure route	Results	Reference
Mammalian*				
Human	Chromosomal abberration	Inhalation	Positive	Martin et al 1991
Human Mouse	Sister chromatid exchange DNA damage	Inhalation Intraperitoneal	Positive Positive	Martin et al 1991 Hu and Zhu 1990
Eukaryotic cells°:				
Human lymphocites Chinese hamster cells Chinese hamster cells	Chromosomal abberration Sister chromatid exchang Chromosomal abberration	in vitro in vitro in vitro	Positive Positive Positive	Fajgelj et al 1992 Lin et al. 1993 Lin et al. 1993
Chinese hamster cells	Micronucleus test	in vitro	Positive	Lin et al. 1993

Table 5. Damage type by U exposure

Body system	Human studies	Animal studies
Renal	Elevated protein excretion, urinary catalase and diuresis	Damage to Proximal convoluted tubules, necrotic cells from tubular epithelium, glomerular changes
Central Nervous System	Decreased performance on neurocognitive tests	Acute cholinergic toxicity; Electrophysiological changes in hippocampus
DNA	Increased reports of cancers	Increased urine mutagenicity and induction of tumors
Bone/muscle	No studies	Inhibition of periodontal bone formation; and alveolar wound healing
Reproductive	Uranium miners have more first born female children	Moderate to severe focal tubular atrophy; vacuolization of Leydig cells

2.4.2. Radon

Rn is a decay product of U and an inert radioactive gas of natural origin relatively common in the earth's crust.

The radioactivity of Rn is measured in Becquerels (Bq).

Its most stable isotope is ^{222}Rn which decays within a few days emitting alpha type ionizing radiation, forming its decay products including polonium-218 (^{218}Po) and polonium-214 (^{214}Po) that emit alpha radiations too.

Rn is considered very dangerous for human health because the alpha particles, if inhaled, can damage cells DNA and cause lung cancer.

The IARC and then WHO have classified Rn as carcinogen to humans (Group 1).

Rn can also be found in drinking water, though in much smaller amount than in the atmosphere; however, it can still be a source of exposure to ionizing radiation for the stomach.

The WHO and the European Commission guidelines recommend an intensification of controls if Rn concentration in drinking water exceeds 100 Bq/l. The United States have proposed a limit of 159 Bq/l for private reserves of water. The European Commission recommends immediate action over 1000 Bq/l. The Italian National Health Council has recommended that in mineral and bottled water Rn concentration should not exceed 100 Bq/l (32 Bq/l for water intended for children and infants).

Water continually releases Rn in atmosphere by volatilization. Hence, groundwater has a higher concentration of ^{222}Rn than surface water because Rn is continuously produced by radioactive decay of ^{226}Radio (^{226}Rd) present in rocks.

2.5. Perchlorates

Perchlorates are released to the environment by a combination of anthropogenic and natural sources, as they are naturally present on earth and they are also generated as by-products of water chlorination systems (see paragraph 3).

There are five perchlorate salts: magnesium, potassium, ammonium, sodium, and lithium perchlorate.

Perchlorates have been found in lakes, rivers, and groundwater wells and this has recently received high attention in the U.S.A.

Perchlorate contamination of ground and surface waters, in fact, has placed U.S. drinking water resources at risk, especially in the West.

There are few studies on potential risks due to exposure to perchlorates.

However, concerns were highlighted in disputes between the U.S.EPA and the Pentagon regarding the regulation of perchlorate, because it is a fuel component for rockets.

The U.S.EPA has developed a lifetime exposure precautionary limit intended to prevent adverse effects on child's development, thus recommending the use of a provisional purification level for this water pollutant in the range of 4–18 ppb [43, 44].

The detection of perchlorate in drinking water supplies and in tap water samples (ranging from 4 to 420 μg/L) indicates that the general American population may be exposed through drinking water.

Perchlorate is not dissolved or modified inside the body and reaches the thyroid gland in a few hours.

Perchlorates can cause competitive inhibition of iodide uptake by the thyroid gland, disrupting thyroid hormone levels that are responsible for regulating many of the body’s metabolic and developmental functions.

The hypothyroidism caused in animals by chronic exposure to perchlorate may lead to thyroid tumors.

The IARC has not classified the perchlorates as carcinogenic substances whereas EPA has asserted that perchlorates are likely not to pose a risk of thyroid cancer in humans.

These assertions are based on limited information regarding the route of exposure to perchlorate and, as yet, there is no study about the effects in humans or animals due to dermal exposure to perchlorate.

Water treatment technologies for the removal of perchlorate commonly used are: chlorination, ion exchange, membrane processes, electrodialysis and reverse osmosis [43].

Perchlorates are regulated in the U.S. and Canada while there is no limit value in the WHO, European and Australian guidelines. As a consequence, the presence of perchlorate in drinking water wrongly is considered a “local problem”.

2.6. NITRITES AND NITRATES

Nitrates are well-known water pollutant harmful to human health because they are teratogenic and carcinogenetic substances (cardiac defects, stomach cancer); more toxic are nitrites originating from them through the action of enzymes present in the human body [11].

Carcinogenic N-nitroso compounds, suspected of high carcinogenic potential, are formed from nitrites.

The most well known health hazard associated with high levels of nitrate in drinking water is methaemoglobinaemia or blue-baby syndrome.

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 (< 1 year) should take only bottled mineral water.

The EC and the 1996 NHMRC Australian Drinking Water Guidelines limit the concentration of nitrate in public drinking water supplies to a maximum of 50 ppm [45].

EPA has established 10 mg/L as a maximum contaminant level (MCL) for nitrates in drinking water.

It been shown that chlorination lowers the risk to human health associated with exposure to nitrates.

2.7. METHYL TERTIARY BUTYL ETHER (MTBE)

Since the late 1970's in the U.S.A. MtBE has been used as an octane enhancer in gasoline.

MtBE is a volatile organic chemical and an anthropogenic contaminant; due to its small molecular size and solubility in water, it moves rapidly into groundwater [46].

It can enter surface water and groundwater through wet atmospheric deposition or as a result of fuel spills.

In urban areas, particularly, varying concentrations of MTBE have been identified in rain water and surface water [47].

Squillace and colleagues (1997) estimated that in some urban areas the MtBE concentration in rain water is approximately 3μg/L. Instead, highest concentrations have been found in drinking water, ranging from 20μg/L to 200μg/L [47].

There are no studies about effects on humans due to long-term exposure to MtBE, as all available studies on hazard assessment are on animals.

Specifically, studies on MtBE carcinogenicity are only in rodents.

In Belpoggi’s study [48], oral exposure caused a dose-related increase in the incidence of leukemia and lymphomas in the female rats and an increase in Leydig cells adenomas in male rats; however, this study poses big limitations if we want to assess risks from drinking water exposure.

In fact no is found a statistically significant association between MtBE and Leydig cell tumor in rats, thus, this data for Goodman and collegues do not support a causal association between MTBE exposure and Leydig cell tumor [49].

In conclusion, carcinogenicity data support that MtBE is a potential carcinogenic for humans at high doses [50].

Chapter 3

MUTAGENS AND CARCINOGENS POLLUTANTS IN DISINFECTED WATERS

The presence of microorganisms in water can cause many diseases (e.g. hepatitis, cholera, typhoid fever, dysentery). These diseases have killed many people throughout the world in the last century and continue to mow down a huge number of human beings in third world Countries.

Disinfection has been the best prevention to avoid waterborne diseases.

Disinfection of tap water could be considered a significant public health success; in fact it has made possible the reduction of the incidence of waterborne diseases in all industrialized countries.

UV and various chemicals are used for water disinfection (e.g. chlorine gas, chlorinated lime, sodium hypocloride, active chlorine, chloramines, ozone, and more).

Chlorination is currently the most widely used chemical water treatment in the world; generally the use of hypochlorite ion (ClO^-) is preferred to chlorination by chlorine dioxide (ClO_2) and chlorine gas (Cl_2) [2].

Ozone (O3) used as disinfection agent is becoming widespread due to its powerful oxidizing properties and effectiveness in the inactivation of micro-organisms recalcitrant to disinfection by chlorine [51].

All disinfection treatments have the disadvantage of releasing disinfection-disinfection byproducts (DBPs), many of which are mutagenic and carcinogenic.

The main determinants in DBPs formation are the quality of water during chlorination and the dose and/or the type of chlorine used .

Surface water contains organic matter (especially humic and fulvic acids) that is the main source of by-products.

The formation of DBPs can be reduced by purifying the water before chlorination and by optimising the chlorine dosage as to be effective but not excessive.

Groundwater does not usually contain organic matter therefore the chlorinated water prepared from ground water contains notably less DBPs.

If the raw water contains bromide ions, brominated-DBPs are formed during chlorination, with higher carcinogenic potency compared to chlorinated-DPBs.

Actually it is not known which DBP in chlorinated drinking water certainly poses cancer risk for man [52]; indeed, people are exposed simultaneously to a mixture of different DBPs via dermal, inhalation, and ingestion routes. At least 600 DBPs have been identified, but only 11 of them are regulated (see Table 6) though differently in many countries of the world. In addition there is lack of data and studies on many of them (iodo-acids, haloacetonitriles, ecc…).

Epidemiological studies have been carried out in order to highlight the possible increase of cancer incidence in populations drinking water treated with chlorine. These studies have shown that there is a relationship between DBPs concentration in drinking water and prostate, intestine and anal cancers [2].

Trihalometanes (THMs), acetic halogenic acids (HAAs), acetonitriles (HANs) and perchlorates (see 2.5) are important DBPs.

THMs are very resistant, mutagenic, teratogenic and carcinogenic substances; chloroform is the best known and the most dangerous.

THMs still represent a major public health problem in relation to the use and consumption of drinking water [53]. They are of great concern because they cause gastrointestinal cancers.

Table 6. Some importants DBPs and correlate cancers

Types of DBPs	Disinfection system	Tissue	Tumors	References
Trihalomethanes (THMs)				
Chloroform	Chlorine	Liver Kidney	Adenoma, carcinoma Adenoma, carcinoma	IPCS1994, IARC 1999b and Sciacca & Oliveri Conti 2009.
Dibromochloromethane	Chlorine	Liver Kidney	Adenoma, carcinoma Adenoma, carcinoma	IARC 1991.
Bromodichloromethane	Chlorine	Kidney Liver	Adenoma, carcinoma Adenoma, carcinoma	IARC 1991, IARC 1999a.
Bromoform	Chlorine	Large int.	Adenomatous polyp. Adenocarcinoma	IARC 1991, George et al. 2002.

Table 6. (Continued).

Types of DBPs	Disinfection system	Tissue	Tumors	References
Haloacetic acids (HAAs) Monochloroacetic acid Dichloroacetic acid Trichloroacetic acid Bromochloroacetic acid Bromodichloroacetic acid Dibromochloroacetic acid Dibromoacetic acid Tribromoacetic acid	All formed by Chlorine and chlorine from Desalination	Liver Liver	Adenoma, carcinoma Adenocarcinoma	IARC 1995, Pereira 1996, and De Angelo 1996. IARC 1995, Pereira 1996, and Richardson 2007.
Haloketones (HKs) 1,1-Dichloroacetone 1,1,1-Trichloroacetone	All formed by Chlorine and chlorine from Desalination “	Skin	Basal tumor cells	Xu 2005; Sciacca & Oliveri Conti 2009.
Haloacetonitriles HANs: Trichloroacetonitrile Dichloroacetonitrile Bromochloroacetonitrile Dibromoacetonitrile	All formed by Chlorine and chlorine from Desalination	Skin Lung	Basal tumor cells Alveolar-bronchio-adenoma	Hajes 1986; Sciacca & Oliveri Conti 2009.
Cyanogen halides Cyanogen chloride Cyanogen bromide	Disinfection by Chloramine	Thyroid	Follicolar adenoma carcinoma	Richardson 2007

Types of DBPs	Disinfection system	Tissue	Tumors	References
Oxyhalides Chlorite Chlorate Bromate	Chlorine dioxide, ipochlorite and ozone	Insufficient data, Thyroid Kidney	Genotoxic Follicolar adenoma Adenoma, carcinoma	Sciacca & Oliveri Conti 2009. Moore & Chen 2006
Aldehydes Formaldehyde Acetaldehyde Glyoxal Methyl glyoxal Isobutyraldehyde Isovaleraldehyde 2-MethyIbutyraldehyde Phenylacetaldehyde	Ozone and MtBe metabolite (Formaldehyde)	Testicle blood	Interstitial cell tumors, Lymphoma and leukemia	Richardson 2007
Halogenated furanones MX ZMX EMX Red-MX Ox-MX BMX3 BEMX1 BEMX2 BEMX3 MCA BMX1 BMX2	All formed by Chlorine and ozone	Thyroid Liver Adrenal glands Lung Skin Pancreas Mammary glands Blood	Follicular adenoma, carcinoma Cholangioma, adenoma Cortical adenoma Alveolar and bronchio-adenoma Basal cell tumor Langerhans'cell adenoma Adenocarcinoma, fibroadenoma Lymphoma and leukemia	Komulainen et al. (1997) Agus et al., 2009

The United States Environmental Protection Agency (U.S.EPA), the WHO, and the European Union (EU) have introduced guidelines for THMs in drinking water. U.S.EPA and EU regulate total THMs concentrations (80 µg/L), while WHO provides guidelines for individual THM compounds [53].

The Canadian THM guidelines fixed a threshold of 350 µg/L that is relatively high, therefore it is under review with a range of 50± 100 µg/L (Health and Welfare Canada, 1992)

In Australia THM limit is 250 µg/L.

In some European Countries the DBPs are restricted to very low levels; in Germany, for example, the limit for total THMs is 10 µg/L. In the EC the drinking water quality standard for total THMs is 100 µg/L under review [54]. Three regulated HAAs (dibromoacetic acid, dichloroacetic acid, and trichloroacetic acid) produce liver tumors in rats, and liver and lung tumors in mice after drinking-water exposures. The induction of liver tumors is confirmed by the De Angelo study [55].

Though haloacetonitriles (HANs), haloaldeydes and halochetons are suspected of mutagenic activity, WHO has not yet set any standards for HAAs concentrations [56]. The chlorine dioxide (ClO_2), instead, releases chlorites, that many studies have confirmed as potential mutagenic and genotoxic.

The EU directive does not includes chlorites as undesirable, while the Italian guidelines considers 200 µg/L the acceptable threshold.

Brominated and iodinated DBPs (by-product of ozone disinfection) are particularly dangerous because they are more carcinogenic and mutagenic than their chlorinated analogs; bromate is the most potent carcinogen in animals.

WHO has proposed a provisional threshold value for bromate of 10µg/L, that has also been adopted by the EC, USA and Canada.

It is estimated that about 30% of the total water mutagenic activity can be attributed to MX. WHO has put MX in the list of substances potentially harmful to humans and it has posed a limit (1.8 µg/L) only for undissolved MX.

MX has been classified by the IARC as possibly carcinogenic to humans.

Many recent studies have confirmed that MX induces oxidative stress, chromosomal aberrations and cell transformation.

In the presence of bromides, brominated analogues of MX are formed with closed (BMXs) and open (BEMXs) ring, having one to three bromine substituents. The BMX compounds for mutagenicity are comparable to the chlorine-substituted MXs [57].

The 2,3,5-tribromopyrrole (a halogenated pyrrole) was identified in drinking water in 2003.

Tribromopyrrole is formed from humic acid, while THMs and HAAS are mostly formed from fulvic acid.

Tribromopyrrole has the same genotoxic potency as MX [58].

Chapter 4

FUTURE PERSPECTIVES ON POTENTIAL WATER MUTAGENICITY AND CANCEROGENICITY

Human activity can sometimes have a strong negative impact on water resources, both qualitative and quantitative, in fact in addition to pollution, the total quantity of water available at any given time is an important factor of water managment.

Water pollution is one of the main concerns of the world today. The governments of many countries have striven to find solutions to this problem.

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.

Integrated Water Resource Management therefore goes beyond the traditional description of the resource (integration of use, integration of demand, integration with the environment and with the people).

As we have seen in this chapter, many mutagenic and carcinogenic molecules in water resources can result from environmental contamination, but also from the processes of water sanification.

Through disinfection we want to prevent the much more severe risks due to the presence of pathogens in water; as a result, it is of vital importance to know well the molecules that are formed during contamination as well as from processes of drinking water disinfection in order to properly set the necessary treatments for their removal from water resources.

But then, the different purposes for which water is used (agriculture, industries, for people and livelihoods) demand coordinated policy making and management, in order to avoid possible water contamination.

Priority about water and their relative importance greatly vary from one place to another; nonetheless, all water resources policies in the world should absolutely consider the following issues:

1. Conservation of the water environment and its biodiversity.
2. Sustainable use of the water resources.
3. Requests control and promotion of a water conservation program.
4. Regeneration and reuse the waste waters [59].

Sustainable solutions have to be identified case by case, with the objective of minimizing the risk, and throughout the involvement and consensus of all stakeholders. For this reason, the development of risk assessment and management methodologies has been internationally regarded as having a crucial role.

It is only from common efforts by all stakeholders worldwide on those two directions that we can hope that not only all people throughout the world in the next future, but also our future generations can be assured of the necessary water resources.

It is advisable that these topics should be the primary goals of scientific research for obtaining greater certainty and safety of water resources.

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