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Focus on Bisphenol A, an Uncertain Environmental Pollutant

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1. Introduction

Bisphenol A (BPA) is a ubiquitous chemical found in many consumer products. Despite the growing link between BPA and several diseases, including various cancers, it remains unregulated in many countries (like the USA).

BPA has a high industrial production-volume that started in the USA in 1957, but by 2001 was estimated to be globally approximately 2.5 million tons. It is widely used mainly in the production of polycarbonate (PC), plastics and epoxy resins, but also for many other applications (see Fig.1.) (Pfeiffer et al., 1997). Over 95% of BPA world consumption in 2009 was for those two purposes.

The PC applications include adhesives, compact disks, dental prosthesis and sealants, electrical and electronic parts, returnable empties, refillable water bottles and items for food such as sport bottles, baby bottles, pitchers, tumblers, home food containers and flatware. The epoxy applications include the protective coatings for the interiors and exteriors of food and beverage containers, as well as dental materials. BPA is also present in recycled and thermal paper (Keri et al., 2007; Ishido et al., 2004; Loffredo et al., 2010).

Because of those uses, consumers of canned food or infants being bottle fed are particularly exposed to BPA through their diet, though many other sources (environmental and occupational) of human exposure are proposed today by researchers.

BPA has drawn much discussion about its safety, due to its persistence in our environment (water, air, dust, waste sludge, food etc.) (Huang & Leung, 2009).

A variety of studies are available on BPA concentration in food (from food surveys) and BPA migration from contact with food including via baby bottles and dental materials, and BPA concentration in air, dust and water. There are also a limited number of studies available on BPA concentration in paper (FAO-WHO, 2010; Reuben, 2010).

A number of studies have involved BPA as a potential "endocrine disrupter," primarily on the basis of the results of in vitro exposure, that, however, have not been unequivocally confirmed in vivo.

Studies on the effects of BPA on health have focused on its oestrogenic activity, but some reports have also highlighted additional modes of its action, including liver damage,

disrupted pancreatic β-cell function , thyroid hormone disruption and obesity-promoting effects (Karim & Husain, 2010; Keri et al., 2007).

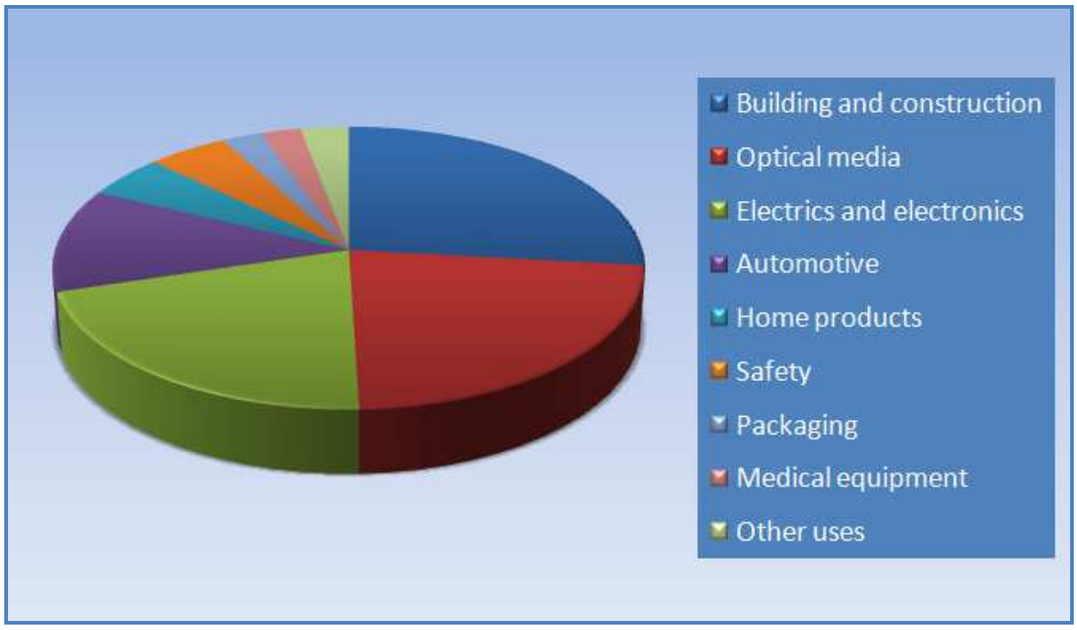

Fig. 1. European applications of BPA

BPA alters the cycle of the epithelial cells of the mammary gland in experimental mice and in human cells (in vitro) (Colerangle & Roy, 1997). It has received considerable media coverage, thus the problem is well known by the Western population, so much so that consumers have shown concern about BPA's oestrogenic effects.

All levels of government, from global to local, work to protect people from diseases through rigorous regulation of environmental pollutants (Dekant & Völkel, 2008; FAO-WHO, 2010). In the light of today's uncertainties about the possibility of the adverse human health effects at low doses of BPA exposure (especially on reproduction, the nervous system and behavioural development) and considering the relatively higher exposure of very young children compared with adults, the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) jointly organised an expert meeting to assess the safety of BPA (FAO-WHO, 2010).

2. Bisphenol A

BPA, or 4,49-(1-methylethylethylidene) bisphenol, was first synthesised in 1905 (Fig. 2). It is obtained by condensation of phenol with acetone in the presence of a strongly acidic jelly-like ion-exchange resin as a catalyst.

Bisphenol A is a moderately water-soluble compound (300 mg/L at room temperature) and it dissociates in an alkaline environment (pK_a 9.9–11.3). It shows a weak acute toxicity for aquatic biota (Yamamoto et al., 2001).

It is used as a component of plastics, e.g. polyvinyl chloride, and as an antioxidant in glues, epoxy resins and ink.

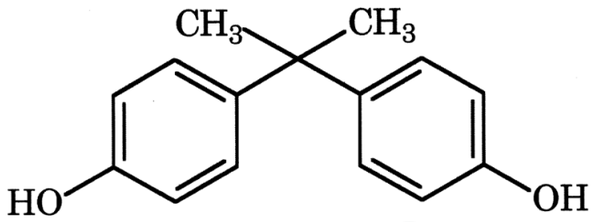

Fig. 2. Bisphenol A

Epoxy resins, in particular, are used as protective linings for a multitude of canned foods and beverages, and as a coating on metal lids for glass jars and bottles, including containers used for infant formula.

Materials containing BPA have been used for many applications in other packaging used for storage of food products, beverages and pharmaceuticals.

PC has been commonly used also for production of components of medical equipment (for dialysis and blood oxygenation), of returnable bottles for soft drinks, of infant feeding bottles, of kitchen dishes, toys, water pipes and polyethylene terephthalates or PET (Cobellis et al., 2009; Keri et al., 2007; Rykowska & Wasiak, 2006).

The wide use of polycarbonates arises mainly from their particular properties: light weight, durable, high tensile strength, very good elasticity, high melting point and high vitrification temperature (Rykowska & Wasiak, 2006).

2.1 Exposure routes to BPA

It is important to note that the border line between occupational and environmental contaminants is very fine and often difficult to demarcate with accuracy.

Many known or suspected carcinogens, in fact, were first identified by studying industrial and agricultural occupational exposures, while later they were found in the environment and in numerous consumer products.

Human exposure to BPA may arise, then, also out of BPA leaching from those materials into the saliva or may occur through skin contact (Cobellis et al., 2009; Keri et al., 2007; Takahashi et al., 2001).

Generally, higher doses are found in small groups due to exposure in their workplace, whereas environmental exposures are found at lower doses but in large populations.

Very few studies have been done on the environmental occurrence of BPA. Recently, the Environment Agency of Japan reported that environmental pollution by BPA is widespread in Japan. BPA has been, in fact, also found in sediments and fish (Yamamoto et al., 2001).

Many studies show that levels detected in beverages are lower than levels in food, levels in fruits are lower than in vegetables, while levels in fatty foods are higher than levels in all other foods. Data also exist on BPA levels in tap water and bottled water (FAO-WHO, 2010).

BPA concentrations in air and dust are widely distributed and there is no difference between indoor and outdoor air.

Few studies have been carried out on BPA in paper packaging, paper treatment water and thermal paper. BPA levels were detected higher in recycled paper than in virgin paper, therefore, additional studies on BPA migration from paper packaging to food are needed (FAO-WHO, 2010).

When waste plastics containing BPA are buried in a landfill a hydrolytic or leaching process may occur to release the BPA from waste to leachate. Landfill leachates are therefore also an important source of environmental BPA (Yamamoto et al., 2001).

As BPA can arise out of those sources, human exposure to this compound occurs especially in urbanised and industrialised areas.

EFSA in 2006 set the Tolerable Daily Intake (TDI) at 0.05 mg BPA/kg body weight (b.w.)/day.

In 2008, EFSA, following more recent studies, reaffirmed the same TDI (EFSA, 2010).

Small amounts of BPA can potentially leach out from food containers into foodstuffs and beverages, and therefore be ingested; as a consequence, in the European Union (EU), BPA is permitted in plastics for food only if the specific migration limit of 0.6 mg/kg of food is respected (see Directive 2002/72/EC relating to plastic materials and plastic materials intended to come into contact with food).

The use of BPA in food contact materials is also authorised in other countries like the USA and Japan.

The new EU implementing Regulation No 321/2011, has replaced Directive 2002/72/EC, making it clear that BPA is "not to be used for the manufacture of polycarbonate baby bottles for feeding infants".

Although FDA and EFSA ruled in 2008 that BPA is safe even for infants, in the same year Canada took a precautionary approach classifying BPA as ''toxic'' under the Canadian Environment Protection Act and it has banned its use in baby bottles and infant formula cans. More than 20 states in the USA are following suit with proposed or enacted BPA bans.

In January 2010, FAO acknowledged that there is concern about BPA's effects, but concluded that there was insufficient scientific evidence to support a product ban or even a requirement to label BPA-containing products.

Endocrine disruptors (EDs) represent a major toxicological and public health issue.

Endocrine disruptors are an extensive group of natural or anthropogenic organic molecules that act as hormone-like substances; they are widely dispersed in the environment and are capable of mimicking the action of steroidal oestrogens (Keri et al., 2007; Ishido et al., 2004; Loffredo et al., 2010).

Among endocrine disruptors BPA is a known xenoestrogen (Ishido et al., 2004).

Studies in vivo have shown that BPA can mimic 17β-estradiol in stimulating prolactin secretion, inducing growth and differentiation and exhibiting uterotrophic activity in rats and mice (Ishido et al., 2004), however, BPA oestrogenicity in vitro has been observed to be 15,000 times less active than 17β-estradiol.

It is important to highlight that oestrogens are important in the maintenance of human pregnancy and the placenta is its major site. BPA is capable of potentially reducing oestrogen synthesis by down-regulating CYP of placental cells (Huang & Leung ,2009).

Studies of prenatal exposure to BPA have shown in mice changes of the gross ovarian anatomy (a reduction in the number of corpora lutea and an increase in unilateral or bilateral ovarian bursae). Others have reported that BPA exposure increases aneuploidy and this has been linked to miscarriages also in humans (Huang & Leung, 2009).

2.1.1 Environmental exposures to BPA

Assessing health hazards due to drinking water contamination is difficult, since it is usually challenging to estimate the levels and timing of exposures, and the specific chemicals involved. It can also be difficult to clearly define exposed populations. Furthermore, it is often not possible to identify the cause of observed health effects when there are multiple exposures or to link specific health effects with an individual chemical that occurs in mixtures (FAO-WHO, 2010; Reuben 2010; Sciacca & Oliveri Conti, 2009).

Many bottled water users assume that it is cleaner than tap water, but BPA can leach from the bottle itself into the water it contains (Reuben, 2010).

Due to the low BPA vapour pressure, inhalation exposure of the general population will likely have only a minor contribution compared to the overall exposure. Inhalation of household dust containing BPA is unlikely to result in significant uptake of BPA from the lung because the large particles typically encountered in household dust do not penetrate into the low lung. However, house dust may be trapped in the mucociliary layer and may be swallowed resulting in additional oral exposure.

Indirect ingestion (dust, soil and toys) is considered to be approximately 0.03 µg/kg bw per day in infants and approximately 0.0001 µg/kg bw per day in children and adults (FAO-WHO, 2010).

Non-occupational dermal exposures to BPA are considered as rare events, moreover, systemic bioavailability of BPA after dermal application is limited to only 10%.

The mean exposure from inhalation of free BPA (concentrations in indoor and outdoor air) is approximately 0.003 µg/kg bw per day for the general population (FAO-WHO, 2010).

Based on this evidence, several government organisations have concluded that oral exposure through food is the major source for BPA exposure in all age groups of non-occupationally exposed human subjects (Reuben, 2010).

Some additional oral exposure to BPA may also result from using BPA-based resins in dentistry, but this is restricted to a short period after treatment with BPA-based dental sealants or composites.

Due to the wide range of applications of BPA in food cans and materials for packaging for food commodities, food may significantly contribute to human BPA exposure.

The EU estimated daily exposures to BPA from a minimum of 0.02 µg/kg bw/day to 59 µg/kg bw/day in adults. The EFSA estimated intakes of BPA through food from 0.2 µg/kg bw/day (a three month old infant fed with only breast milk) to 13 µg/kg bw/day (a six

month old infant fed with polycarbonate bottles and commercial food). Exposures to BPA based on direct food analysis and food consumption patterns generally resulted in estimates of low daily human exposure ranging from 0.005 to 0.37 µg/kg bw/day (Dekant & Völkel, 2008; EFSA, 2010; FAO-WHO, 2010; Reuben, 2010).

2.1.2 Foetal exposure to BPA

Recent data from epidemiological studies have suggested that perturbations in the foetal environment may predispose individuals to disease and/or organ dysfunction, that becomes apparent in adulthood.

This theory on the foetal origins of adult diseases has prompted scientists to hypothesise that foetal exposure to environmental oestrogens has increased incidence of uterine leiomyoma, testicular cancer and breast cancer as observed in European and US populations over the last 50 years.

Exposure of rodents to low doses of BPA during foetal development has been shown to alter a variety of biological endpoints including early vaginal opening, early onset of puberty, disrupted oestrous cyclicity and decreased levels of luteinising hormone after ovariectomy. These results give strong credence to the supposition that there is a link between foetal exposure to BPA and the development of neoplasias in the adult mammary gland.

These neoplasias may have their origin in the altered morphogenesis that occurs in the foetus during the period of BPA exposure (FAO-WHO, 2010; Murray et al., 2007; Reuben, 2010).

Emerging evidence is that BPA affects the developing brain in the foetus, leading to severe behavioural alterations. Therefore, the hypothesis that BPA might also contribute to the incidence of neurodevelopmental disorders such as attention deficit, hyperactivity disorder and autism has been posited (Ishido et al., 2004).

However, for EFSA, the foetal exposure and also the exposure to total BPA through lactation appear to be limited (EFSA, 2010).

The recent final report of the US National Toxicology Program (NTP) stated that "*there is currently insufficient evidence to conclude that Bisphenol A exposure during development predisposes laboratory animals to develop obesity or metabolic diseases such as diabetes, later in life...*" (EFSA, 2010; Reuben; 2010).

2.1.3 Potential dietary exposure for infants aged 0 to 3

The estimated maximum BPA migration from PC baby bottles is 15 µg/kg. This intake is considered to be safe for consumers.

Infants fed with canned liquid formula in PC bottles, were exposed to 4.5 µg/kg bw per day with a mean of 2.4 µg/kg bw per day, whereas infants fed with powdered formula (prepared when needed) were exposed to lower levels (2.7 µg/kg bw per day with a mean of 2.0 µg/kg bw).

When infants were fed with canned liquid formula in PC-free bottles, the estimates were 0.5 µg/kg bw per day at the mean and 1.9 µg/kg bw per day at the 95th percentile, whereas the

estimates were lower, 0.01 and 0.1 µg/kg bw per day, respectively, for infants fed with powdered formula.

Therefore, the difference between canned liquid and powdered formula is mainly caused by the migration of BPA from the epoxy resin coating the cans in which liquid formula is packaged.

Hence, it has been estimated that the major sources of exposure in this age group are:

- migration of BPA from PC bottles (81%),
- infant liquid formula packaged in PC containers or metal cans with epoxy linings (19%),
- epoxy resin in contact with powdered milk formula (1%).

For children aged 3 and older, the main source of exposure is instead migration from canned food that contributes to 94% of the total exposure (FAO-WHO, 2010).

3. Metabolism and toxicokinetics

BPA is well absorbed from the gastrointestinal tract with conversion to Bispenol A – glucuronides and Bispenol A-sulphate; this phase is critical but not very important because unlike the aglycone-BPA (i.e. free or unconjugated) BPA- glucuronides does not bind to the oestrogen receptor (see Fig.3). Aglycone-BPA does not accumulate in the body.

Glucuronide-BPA is subjected to biliary excretion, enterohepatic recirculation and principally to faecal excretion; humans excrete conjugated forms of BPA in the urine within 6 h (see Fig.3) (FAO-WHO, 2010; Keri et al., 2007).

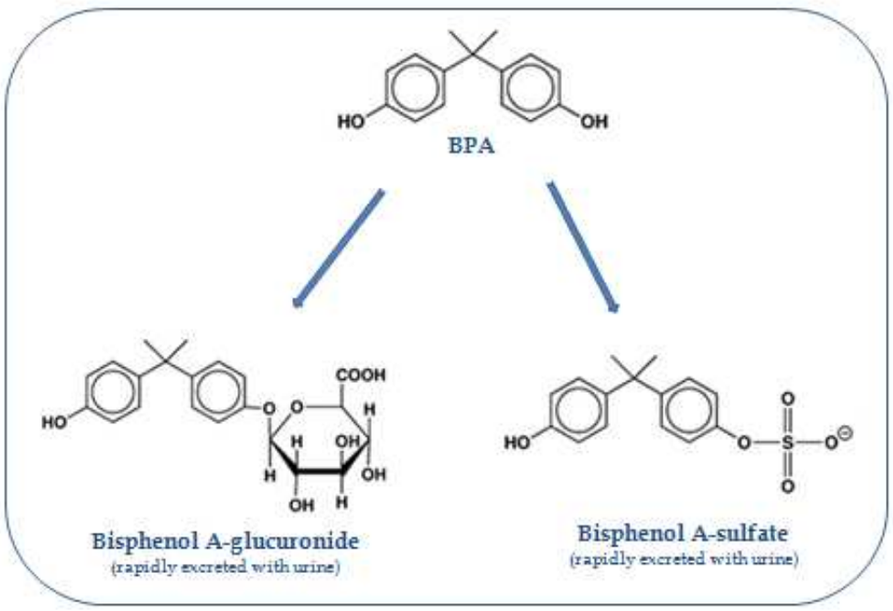

Fig. 3. Biotransformation of bisphenol A in humans to bisphenol A-glucuronide and bisphenol A-sulfate.

4. Mutagenicity and genotoxicity of BPA

Nitrosylation reactions have been associated with the production of several carcinogens, many of which elicit cancers in humans and animals.

Several mutagens have been found by nitrosation of phenol derivatives present in several foodstuffs, including soy sauce, smoked foods, etc.

It has been proven that BPA can be activated into a mutagenic species through nitrosylation reactions, raising the possibility that migration of BPA from polycarbonate or epoxy-lined containers into nitrite-containing foodstuffs could lead to the formation of mutagenic compounds. There is also the possibility that ingestion of BPA in addition to a nitrite-rich diet could lead to the production of mutagens. However, this contribution of nitrosylated-BPA is a new hypothesis of carcinogenesis that is still speculative.

No epidemiological studies have found that BPA is correlated with cancer incidence in the human population, especially with gastric or oesophageal cancers that can be indicative of dietary exposure to nitrosylated mutagens.

The native BPA is non-mutagenic, however the incubation of BPA with sodium nitrite in an acidic environment activates the BPA into a direct-acting frameshift type and base pair mutagen in a variety of sites of nucleic acid in the Ames Salmonella assay (Schrader et al., 2002).

It has been stated that BPA is not likely to pose a genotoxic hazard to humans (FAO-WHO 2010; Keri et al., 2007), although there is only limited data available on the genotoxicity of BPA in human cells (Takahashi et al., 2001).

5. Carcinogenicity of BPA

There are no human epidemiology studies in the existing literature that have produced relevant data for the assessment of the carcinogenic potential of BPA (Haighton et al., 2002). BPA may be associated with increased cancers of the haematopoietic system, breast and a significant increase in interstitial-cell tumours of the testes. DNA adducts generally are formed in target mammary cells. Although DNA adducts do not necessarily evolve into tumours or other chronic degenerative diseases, the formation of these molecular lesions in target mammary cells may have relevance for the potential involvement of BPA in breast carcinogenesis (Izzotti et al., 2009). In addition to forming DNA adducts itself, BPA may act indirectly by unbalancing oestrogen metabolism; these effects could be additive, increasing even further the risk of BPA to initiate cancer (Cavalieri & Rogan, 2010).

BPA alters microtubule function and can induce aneuploidy in some cells and tissues. It has been speculated that the ability of BPA to induce aneuploidy may play a role in the development of cancer (Takahashi et al., 2001) but also low doses of BPA generate reactive oxygen species (ROS) by decreasing the activities of antioxidant enzymes and increasing lipid peroxidation, thereby causing oxidative stress in the liver of rats (Bindhumol et al., 2003).

Extensive research has revealed that the oxidative stress can lead to chronic inflammation, which in turn could mediate most chronic diseases including cancer, diabetes and cardiovascular, neurological and pulmonary diseases. The oxidative stress activates the inflammatory pathways leading to transformation of a normal cell to tumour cell (Kamp et al., 2011; Reuter et al., 2010).

Early life exposure to BPA may induce or predispose to preneoplastic lesions of the mammary gland and prostate gland in adult mice, but this is not yet demonstrated in humans; also prenatal exposure to environmental doses of BPA alters the mammary gland development in mice, increasing the endpoints considered markers of breast cancer risk in humans. Investigators funded by the US National Institutes of Health (NIH) concluded that a strong correlation is found between the above-named exposure, cancer and early puberty. Several studies aimed at demonstrating the increases of some tumour types after BPA exposure were considered not to provide convincing evidence for carcinogenicity.

BPA exposure during the perinatal period is important because it has been hypothesised that it could alter the prostate and mammary gland development, predisposing to neoplastic or preneoplastic conditions (see section 2.1.2) (EFSA; 2010; FAO-WHO, 2010).

In any case the European Commission, in addition to known carcinogens, includes BPA in the lists of chemicals that are “of concern".

6. Reproductive and developmental toxicity of BPA in mammalian species

Emerging evidence has proposed a putative role for ubiquitous environmental contaminants in the occurrence of endometriosis. The mechanism of action may be carried out through the interaction with steroidal receptors, mimicking an oestrogenic effect (Cobellis et al., 2009).

Bisphenol A has been proven to have oestrogenic activity, even at concentrations below 1 ng/L. A study on mice revealed that a concentration of BPA as low as 20 ppm in drinking water is sufficient to bring about genetic changes in mice foetuses. The changes are a result of disturbance of the distribution of chromosomes in the daughter cells (Rykowska & Wasiak, 2006). The US Center for the Evaluation of Risks to Human Reproduction concluded in 2008 that there is “some concern for effects on the brain, behaviour, and prostate gland in foetuses, infants, and children at current human exposures to bisphenol A”.

Several governing agencies, recently, have identified an oral reproductive and developmental NOAEL of 50 mg/kg bw per day (FAO-WHO, 2010).

7. Conclusions

Much remains to be learned about the effects of BPA environmental exposure on cancer risk. Based on what is known, however, there is much that governments and industry can do now to address or prevent environmental cancer risk.

At the same time, individuals can take important steps in choices of lifestyle to reduce their exposure to environmental elements that increase risk of cancer and other severe diseases.

Furthermore, the individual’s small actions, if considered collectively, can drastically reduce the number and levels of environmental contaminants.

Some alternatives to BPA-containing materials for PC bottles and containers, and epoxy can linings are available on the world's market or proposed for domestic use. The functionality and safety of any replacement material need to be carefully assessed before use or sale.

However, as it appears that it will not be possible to identify a single replacement for all uses of BPA, particularly for can coatings, the problem is still open.

Due to the gaps in the current literature, it is premature to conclude that BPA is certainly a carcinogenic, however, the evidence suggests that BPA increases cancer susceptibility through developmental reprogramming and changes in target organ morphogenesis as a result of epigenetic alterations. It is important to underscore that studies examining changes in carcinogenic susceptibility have only focused on the mammary and prostate glands, two obvious targets of potential endocrine disruption, but it is necessary to include vagina, uterus, ovary and testes.

Usually, the main exposure route for humans to low environmental doses of BPA is orally. There is no doubt that BPA is an environmental pollutant, although it is not yet considered a carcinogen, therefore the ALARA (As Low As Reasonably Achievable) concept should be employed for protection of consumers and the general population.

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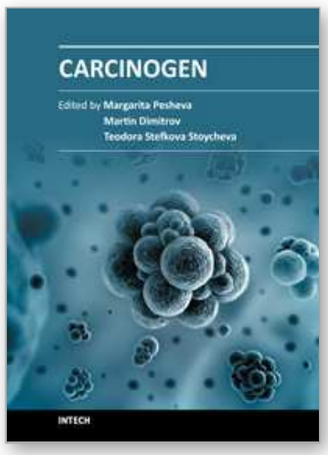

Carcinogen

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During the last decades, cancer diseases have increased all over the world. The low quality of food and strong pollution of environment are the main prerequisites for carcinogenesis. The main problem for scientists is to find strategy for prevention of cancer diseases. Therefore, the information about the models for studying carcinogenesis and mutagens which appear during cooking, environmental pollutants, and tests for specific detection of carcinogens is particularly important. The book "Carcinogen" is intended for biologists, researchers, students in medical sciences and professionals interested in associated areas.

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