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Bisphenol a: An endocrine disruptor

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Abstract
Bisphenol A (BPA) is an organic compound classified to the group of phenols. This compound is synthesized by the condensation of acetone (hence the suffix A in the name) with two equivalents of phenol. Bisphenol A (BPA) is a multipurpose compound that is widely used in the modern industrial world as a component of polycarbonate plastics and epoxy resins and is one of the highest volume chemicals produced globally. BPA has specific health effects like structural and neurochemical changes throughout the brain like hyperactivity, learning deficits, increased aggression and increase likelihood of drug dependency. BPA can also cause polycystic ovary syndrome (PCOS), which is a common endocrine disorder, affecting between 4% and 8% of reproductive aged cattle, goat, dog, and women. We need to be aware about deleterious effects of bisphenol A containing plastic and try to minimize its use in our daily life.

Keywords: Bisphenol A, polycarbonate plastics, health effect, cancer

Introduction
Over the past decade, a growing body of evidence suggests that numerous chemicals, both natural and man-made, may interfere with the endocrine system and produce adverse effects in humans, wildlife, fish or birds. These chemicals are often referred as "endocrine disruptors". These chemicals are present in products of daily use like plastic water bottle, plastic food containers, baby feeding bottles, flame retardants, plastic toys and cosmetics and many other chemicals. Endocrine disrupters interfere in the production and normal physiological functioning of hormones in the body of man and animals and produce various endocrine disorders. This interference may be at the level of development of endocrine system, reproductive status of animal and normal functioning of immune system etc. They may increase or decrease hormone secretion, alters hormone signaling or bind to the essential hormones, thereby altering normal hormonal status of individual.

A large number of chemical substances can cause endocrine disruption includes PCBs, DDT, dioxin, atrazine, phthalates, perchlorate, mercury, organophosphate insecticide etc. Chemicals like Bisphenol A are considered as major contributor of endocrine disruption in man and animals. It is a manmade organic chemical of phenol group. Laboratory animal studies have shown its significant endocrine disruption potential. Bisphenol A leaches from the plastic container into the food, thus enters in food chain. Its name according to the International Union of Pure and Applied Chemistry (IUPAC) is 4,4'-dihydroxy-2,2-diphenylpropane [12]. This compound is synthesized by the condensation of acetone (hence the suffix A in the name) with two equivalents of phenol. This reaction is catalyzed by a strong acid, such as hydrochloric acid (HCl) or a sulfonated polystyrene resin. It is a colorless solid that is soluble in organic solvents, but poorly soluble in water [15]. Molecular weight of Bisphenol A is 228 gm/mole and its empirical formula is $(CH_3)_2C(C_6H_4OH)_2$. Bisphenol A was first synthesized by the Russian chemist Alexander Dianin in 1891 and has been in commercial use since 1957.

World production capacity of Bisphenol A was 1 million tons in 1980s [5] and more than 2.2 million tonns in 2009. Bisphenol A (BPA) is a component of polycarbonate plastics and epoxy resins and is one of the highest volume chemicals produced globally. Widespread application of bisphenol A in plastic industry led to an increased demand for this chemical substance and in consequence may pose a greater risk to human and animal health.

Sources of Bisphenol A
About 67% of the bisphenol A produce, is used to make polycarbonate, and approximately 30% is used in epoxy resin production. The remaining 3% is used in other products. Polycarbonate plastic is used to make a variety of common products, including baby and water

bottles, sports equipment and medical devices. These plastics are typically clear and rigid. Epoxy resins are used as coatings to line the inside of almost all food and beverage cans to prevent the contents from reacting with the metal. BPA can migrate into foods from cans and from polycarbonate plastic products such as baby bottles, tableware, and food containers [10]. Warming the plastic, such as in a microwave, increased the leaching of BPA into liquids; temperature appears to be a more important factor in leaching than the age of the container.

Routes of Exposure to Bisphenol A

Bisphenol A may enter the animal and human body by ingestion, inhalation or dermal contact. However, it is believed that the main exposure of animals and humans to BPA occurs by ingesting foods and drinks contaminated with bisphenol A from polycarbonate bottles and cans coated with epoxy resins.

Dietary exposure

Bisphenol A is well absorbed by the oral route. Due to its properties, bisphenol A can be easily released from the polymer product, in which it is present, and migrate into the environment. The ester bond connecting the BPA molecules in polycarbonates or epoxy resins is hydrolyzed during heating or in acidic or alkaline medium. As a result, free BPA is released and migrates into the food, beverages and into the environment. In addition, migration is enhanced by repeated washing with detergents, rubbing and sterilization [12]. In a study, on food storage cans, coated with epoxy resin under conditions corresponding to the sterilization process (canning), significant amounts of BPA, 70–90 μg BPA per 1 kg of the medium were detected in the preserved foods or model liquids [12].

Environmental exposure

Dust and air

Bisphenol A may be present in the dust. It is believed that dust may be important in the case of exposure of children, who are playing on the floor and frequently happen to put hands into their mouth. However, because of the low vapor pressure of bisphenol A, inhalation exposure to this compound is likely to be a small part of the overall exposure. Assuming complete BPA absorption by the lungs, the estimated daily exposure to BPA is 0.008–0.014 μg/person/day, while the daily exposure to BPA by eating foods contaminated with BPA is 1.7–2.7μg/person/day [3] so the inhalation exposure is about 200 times lower than the dietary BPA intake with food.

Water

Bisphenol A is often found in water at concentrations of the order of a few ppm. Bisphenol A and also other endocrine disruptors, are not completely eliminated from the effluents during their processing in the wastewater treatment plants. Bisphenol A may be also released from the soil and contaminate ground water. Daily intake of bisphenol A with drinking water may be negligibly low compared to the consumption with beverages and food products in contact with BPA-containing wrappings [18].

Other sources of exposure

Dental materials

Other source of BPA, which may influence the risk of exposure includes dental materials. It is likely that bisphenol A, as a pollutant formed during the synthesis of dental fillings, can be released to the human saliva through enzymatic hydrolysis by esterases found in saliva [16]. Yang *et al.* (2014) observed that BPA is detected in saliva 1h after filling the defect, and becomes non-detectable after 3h, whereas in serum it is not detectable after 24h. In saliva, the concentration of BPA ranged from 5.8 to 105.6ppb whereas the concentrations in saliva ranged from 3.3 to 30ppm [18]. These differences could be due to different quantities of dental sealant used to fill the defect (8 or 32mg).

Paper

Although not much has been reported about dermal exposure to BPA, the exposure does occur, especially through dermal contact with products containing BPA (e.g., thermal printer paper) [2]. However, dermal exposure is considered to be negligible, since the skin penetration of BPA is below 10%. It is relevant only in the context of occupational exposure, e.g. during production, treatment and processing of BPA, and also direct dermal contact with BPA found on the surface of thermal paper.

Absorption and Distribution

Research published in 2002 shows that when bisphenol A enters the body per os, it is rapidly absorbed in the gastrointestinal tract and is metabolized in the liver and the intestine. Most of the ingested BPA is excreted with the urine in the form of inactive metabolites of bisphenol A glucuronide and bisphenol A sulphate [3] within about 6h ($t_{1/2}$ = 5.4h), and BPA is almost completely eliminated within 24h. Total (free plus conjugated) BPA concentration is often used to assess exposure level to all the sources of BPA [17]. Because BPA is quickly excreted from the body, concentrations detected in human urine and blood may indicate a greater intake of this compound with drinks and food.

Mechanisms of action of Bisphenol A

BPA has been shown in a number of studies to act through several different receptor-mediated mechanisms of action, to disrupt the endocrine system and, it has become a model endocrine disrupting chemical (EDC). BPA is a xenoestrogen that binds to and activates the estrogen receptor (ER). Although it has lower affinity for genomic ER than estradiol, circulating concentrations of BPA are higher than estradiol and are within a biologically active range. In addition, BPA is at least as bioactive as estradiol for a number of responses, particularly those mediated by nongenomic signalling. BPA is also an antiandrogen, in that it binds to the androgen receptor and blocks the normal action of androgens ; it can also alter steroid hormone synthesis and circulating steroid hormone concentrations [11] and it also alter thyroid hormone synthesis i.e BPA inhibit the T_4 (thyroxine) converted to T_3 (triiodothyronine) [14].

Effect of Bisphenol A on Animals

Cattle

Fertility in dairy cows has declined over the last several decades. The recent decline in fertility in high-yielding dairy cows may be due to many factors, but there is evidence that reproductive failure in farm animals may be a consequence of acute or long-term exposure to endocrine disrupting chemicals (EDCs). However, so far this threat to bovine fertility had attracted little attention. EDCs can mimic or disrupt estrogen actions. Estrogen is essential for female reproduction. Effects of exposure to various environmental

endocrine-disrupting chemicals (like PCBs, dioxins, DES, BPA soy, alfalfa) for example, a higher incidence of cystic ovaries, accompanied by irregular estrus and/or anestrus, occurs in cow. Environmental estrogens can affect the formation of ovarian follicles and initiation of follicle growth in bovine ovaries. These processes occur during early to mid gestation in cattle. Exposure to these endocrine-disrupting chemicals (EDCs) during foetal life can affect early ovarian follicular development and thus, potentially affect female reproductive lifespan and also cause the development of cystic follicles *in vivo* and thus, reduces fertility. These outputs may provide useful information for dairy producers and veterinarians to develop better herd management and nutritional strategies to avoid exposing cattle to endocrine disrupting chemicals found to have adverse effects and thus, increase reproductive performance [7].

Goat

Polycarbonate is used in a wide range of plastic products, such as toys and livestock tools, and it leaches out from such products at a rate that increases with repeated use. BPA is always released from a plastic apparatus into feed during repeated feeding or watering in plastic apparatus. BPA at a low concentration in goats tends to lead spermatogenic and sertoli cells to apoptosis, whereas higher concentration tends to lead spermatogenic and sertoli cells necrosis [1].

Dog and Cat

Dogs that chew on plastic training devices and toys may be exposed to hormone-altering chemicals. Bisphenol A (BPA) and phthalates – ingredients of hard plastics and vinyl, readily leach from bumper toys, which are used to train retrieving dogs. Examine dog products as a potential source of exposure for pets. BPA is used to line the metal pet food containers and may enter the canned pet food. After eating canned dog food for two weeks as part of a biomedical study, dogs had higher levels of the bisphenol A (BPA) in their blood than when the research began. Little research exists on BPA's effects on dogs and cats, research on laboratory rodents and amphibians provided evidence that BPA may be associated with prostate cancer, lack of sexual differentiation, declines in sperm quality, learning impairment and other health problems. However, no safe limit for daily consumption has so far, been established for pets. Thermal processing temperature, makeup of the product contents, repeated container uses and pH swings are known to increase the amount of BPA that leaches from plastics [20].

Fish

Aquatic environments such as rivers and streams become reservoirs for contaminants, including BPA. Scientists have determined that fish exposed to endocrine-disrupting chemicals will pass adverse reproductive effects onto their offspring as many as three generations later. BPA causes activation of the oestrogen receptor, Malformation of reproductive organs, decline in sperm quality, retardation of sperm maturity and shifting of gender ratio. Male red shiners show colour variations after swimming in water contaminated with bisphenol A [6].

Effects of bisphenol a on non-mammalian wildlife

Discharge of Bisphenol A into the environment, not only occur from factories producing BPA, but also from numerous factories where BPA is incorporated into plastics or used in other products. Discharges to air are expected to break down fairly rapidly, but discharges to water are likely to be more persistent and more of a problem.

Frogs

There are very little data on the levels of BPA in the aquatic environment, but even at very low exposure levels BPA appears to affect the sexual differentiation of frogs. They found that at a BPA exposure level of 23µg/l there was a significant increase in the number of females, and that a concentration of 2.3µg/l BPA caused a smaller, but not significant, increase in the number of females. Such an alteration in sex-ratios may have an important effect on population levels [6].

Snails

Some workers have shown that exposure to even lower levels of BPA can be harmful. For example, Oehlmann and colleagues have found that BPA, at levels down to 1µg/l, can cause dramatic effects in female freshwater ramshorn snails. BPA apparently stimulates egg production and causes swelling of the female sexual glands which results in blocked ducts. This blockage prevents the eggs from being transported, so that the egg containing gland can be put under so much pressure that it bursts, and effectively these snails are sterilised. In some cases they also die because of the increased risk of infection [13].

Reptiles Reptiles have also shown negative effect when exposed to BPA. In species that have temperature-dependent sex determination. BPA has been shown to induce sex changes in embryos. BPA exposure of 1400µg/l (90µg/egg) resulted in abnormal seminiferous tubules. When egg shells were exposed to higher amount of BPA during critical periods for gender determination, cause alteration in sex-ratios and increase number of females.

Birds

Effect of BPA on birds has shown effect like increased mortality in chicken (*Gallus domestic*) embryos and malformation of reproductive organs. Furaya *et al*. (2002) reported delayed growth of comb, wattle and testes in male chickens that received oral doses of BPA as low as 2µg/1000g body weight every two days for up to weeks.

Health Effects of Bisphenol A

Erler and Novak (2010) observed BPA specific health effects like structural and neurochemical changes throughout the brain (i.e. hyperactivity, learning deficits, increased aggression, increased likelihood of drug dependency). Zhou *et al*. (2008) studied the BPA specific health effects like polycystic ovary syndrome (PCOS) as a common endocrine disorder, affecting between 4% and 8% of reproductive aged cattle, goat, dog, and women. According to Gao *et al.* (2015) studies have shown links between BPA exposure and hormone- related cancers, including breast, prostate, and ovarian cancers and endometrial carcinoma. Erler and Novak, (2010) studies have shows the disruption of hormone production, fertility, and early sexual maturation in males and females.

How to Reduce Exposure to Bisphenol A

Avoid heating food in plastic containers. Heat can release chemicals so avoid heating food in plastic containers. For the same reason, one should only drink cold liquids in plastic containers. Wash plastic containers in mild detergents. Harsh

detergents help liberate chemical from plastics making container much more likely to leach chemicals into food. Avoid using plastic packaging, where you can. For example, bring reusable bags during grocery shopping. Select safe plastics for food storage. Consider switching to glass storage containers since plastic containers can leach chemicals into the environment and your food as they age and become used. Avoid using plastic toys for training purpose in dog. Avoid using pet cane food and drinks to pet, it can reduced the BPA exposure to pet, provide the fresh food, or home cooked food to pet. Never throw of plastic bag packed with vegetables waste food outside or in roads directly because cattle get exposure to BPA by eating this vegetable and food along with plastic directly. Avoid repeated using plastic container in animals for feeding, watering etc. and avoid washing this plastic container with harsh detergent or soap.

Conclusion

We are living in a plastic world. It is nearly impossible in most industrialized nations to avoid daily plastic use. Society's most beloved products including our foods are covered in plastic. Unfortunately, some of the constituents in plastics like BPA leach out into our environment and foods. Plastics have been beneficial for the development of modern civilization but it is time to stop and analyze its deleterious effects on animals, humans and wildlife health. Bisphenol A has the wide range of health effects on animals, humans and other organisms especially involving reproductive health and endocrine health like weight gain, neurochemical change including diabetes and cancer so we need to be aware of these things. I am not in favor of stopping the use of plastics in our daily life actually it is next to impossible, I am only advocating the more rational and informed used of plastic in our daily life so that its deleterious effect or harmful effects can be minimized.

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We declare that we have no conflicts of interest.

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