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Bisphenol A and cattle fertility

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Abstract
From retrospective studies, we have observed that from past few decades the industrialization growing very fast in developed as well as developing countries. This introduced many kinds of products which stamped their deleterious effect on environment, flora and fauna much more efficiently than their useful one. One of them which are recently hot topic for researchers is plastic. Plastic pollution is the major headache and concerning topic for researchers in various aspects like its production and commercial use. The major concern is its efficient as well as harmless disposal because of its harmful chemical composition, which are released during recycling and disposal and are deleterious for environment and living creatures, both. One of such chemicals is bisphenol A (BPA), a phenol group containing organic compound most widely used in industries like polycarbonate plastic, plastic canned food and epoxy resins. It is responsible for many kinds of physiological acute as well as chronic disorders in humans and animals but have the major effect on reproductive system and endocrine disrupter. Effect on bovine reproduction and fertility is of major concern because India became highest milk producer in the world with 198.4 million tones, which is increased by 35.61% from last 6 years. It affects the bovine reproductive system in many ways like affecting the cellular functions and morphology (granulose, theca, cumulus complex etc.) as well as embryonic level too. To maintain such type of high production level it is necessary to properly manage the reproductive performance of bovines. Reproduction is composed of different interconnected cellular and molecular events; such process**is** badly affected at different levels by bisphenol A because of its deleterious effect some country restricted its use and industries become shifted to use bisphenol S (bisphenol A substitute) but after various studies it is proven that it is a "regrettable substitute" rather than substitute. There are many few researches on that field**,** so there is a urge of more and more studies regarding their effect on bovine fertility. By this review we want to make awareness among the people about the dangerous and unwanted effects of such elements on cattle as well as other living organisms also and request researchers to go for future studies and experiments on its other type of unwanted effects not only on the cattle but other living creatures also to prevent further harm to our ecosystem by spreading knowledge and minimizing the use of plastic based products.

Keywords: plastic, bisphenol A, reproduction, endocrine disrupter, bisphenol S, regrettable substitute

Introduction
Livestock sector solely contributes 4.11% of Indian GDP and 25.6% of agricultural GDP. With such contribution, India became highest milk producing country in the world. India is having largest number of livestock as well as bovine population in the world with 536 million and 302.3 million as according to 2019 livestock census. In many researches, bisphenol A (BPA) is proved to having endocrine disrupting property and declared as potential endocrine disrupting chemical (EDC). Afterward its commercial use become restricted in various countries and many industries started to sale their products as "BPA free" (Zalmanova *et al*., 2016) [46]. Such condition propels the industries to substitute BPA with bisphenol S (BPS) because of structural similarities**.** But as early as BPS started being used at commercial level, many studies was conducted on it and it also showed property as EDC so was called "regrettable substitute" with bioaccumulation (Magnusson and Persson, 2015) [23]. Plastic based products not only have these 2 chemicals but thousands of other hidden additives also like lead, phthalates, mercury, dioxins, cadmium etc. and become major area of concern.Still people are using such products blindly because of its durability. We have chosen this topic for review because there is need for further more and more research on the effects of such toxic elements on different body systems with potential treatment and prevention is needed. The most of the economic traits of animals are directly or indirectly linked to reproductive physiology. Bovine oocyte development, follicular dynamics, follicular wave pattern and hormone responsiveness are little bit similar to that of human, so effect of these toxicants on

such structures may be almost same in human as in bovine, so bovine can be used as model for human studies. In some studies, it is found that it badly affects the fertility of both males and females in human. We have discussed here various previous studies on different processes and components like granulose cells, theca cells, connexin 37 protein in cumulus cell, luteal cells, and steroidal hormones and cellular (chromosomal and spindle fibers) component of bovine fertility and reproduction affected by BPA and BPS. There is an urge along with ample of scope for study in bovine reproduction affected by these and many other toxicants.

Bisphenol A (BPA)

Nature

BPA was synthesized first time by Alexander Dianin (Russian chemist) in 1891 and has been commercially used since 1957 (Talpade *et al*., 2018) [37] but before its commercialization it was proved to have potential for imitating estradiol hormone in 1936 (Dodds and Lawson, 1936) [9]. It is phenol containing organic compound, it is synthesized by acetone condensation with 2 phenol groups (Talpade *et al*., 2018) [37]. Its chemical composition is 4, 4'- dihydroxy - 2, 2-diphenylpropane according to International Union of Pure and Applied Chemistry (Mikolajewska *et al*., 2015) [23]. It is a colorless rigid substance poorly soluble in water but soluble in organic solvent, acid, alkali and detergent (Staples *et al*., 1998) [36]. Its molecular weight is 228 gm/mole and chemical formula is $(CH_3)_2C\ (C_6H_4OH)_2$ (Talpade *et al*., 2018) [37].

Mode of entry

BPA is multipurpose compound whose production in increased exponentially in recent years**.** It is used as raw material for wide variety of products like plastic food containers, baby feeding bottles, water bottles, flame retardants, receipt papers, recycling, formularies, cosmetics, plastic toys, etc. (Talpade *et al*., 2018) [37]. Of all the produced BPA, 67% are used for poly carbonated products, 23% for epoxy resin and the rest 3% are used for various other types of products. (Talpade *et al*., 2018) [37]. 90% of Canadian (Bushnik *et al*., 2010) [5] and 92.6% of American peoples. It is transmitted to feed, water, human body and environment (water bodies, soil and atmosphere) directly or through leaching from such products by diffusion, decomposition through heat, acid and alkali treatment (yang *et al*., 2015) [43]. Route of entry of BPA is ingestion (food, water), inhalation (air) and dermal contact. Newborn of human and animals get exposure to this by plastic baby feeding bottle, canned food and liquids (Talpade *et al*., 2018) [37]. Its ester bond is easily broken by application of heat, alkali, acid, UV radiation, hydrolyzing material, detergent, continuous washing, rubbing and sterilization. It is easily absorbed by oral as well as respiratory mucosa including lung. In water it is present in very minute concentration (ppm). Dental filling is also a major source of BPA and its level can be detected in saliva within 1 hr of filling defect but can't be detected after 3 hr, 24 hr in saliva and serum respectively (Talpade *et al*., 2018) [37]. BPA concentration into saliva depends upon amount of filling material used for example if we used 8mg and 32mg of filling material we get 5.8-105.8 ppb and 3.3-30 ppm of BPA respectively (Talpade *et al*., 2018) [37]. Skin penetration of BPA is very low (<10%).

Absorption and distribution

BPA are highly absorbed by oral mucosa and is degraded by salivary esterase enzyme to liberate its monomer which metabolize into liver and intestine, and via blood go to the different systems of body where it produces its effects. It is excreted through urine as inactive metabolites like glucoronide and BPA sulphate. Environmental Protection Agency defines EDCs as agent that interfere many physiological processes like production, metabolism, transport and excretion of endogenous hormones necessary for regulating development, reproduction and homeostasis of body (Kavlock *et al*., 1996) [16].

Bisphenol S (BPS)

Maximum industries shifted from BPA to BPS because in 2010. Canadian government banned import, sale and advertisement of BPA containing baby feeding bottles and then after European union also prohibited the manufacturing of BPA containing baby feeding bottles which was passed in Commission direction in the year 2011. BPS is structurally similar to BPA that's why it became used as BPA substitute but it also has endocrine disrupting property like BPA (Rochester and Bolden, 2015) [31]. BPS detected in 25% urine samples in American population in 2000 and became 3 times increased in the year 2014 (Ye *et al*., 2015) [44]. Other studies detected BPS in 81% of urine samples from US and 7 Asian countries (Liao *et al*., 2012) [21]. Now BPS is widely used, despite of having dangerous negative impacts on health (Rochester and Bolden 2015) [31]. Some studies shown that leaching efficiency from products to environment is less for BPS than BPA (Vandenberg *et al*., 2009) [39] but various studies depicted its better skin penetration and less biodegradability than BPA (Liao *et al*., 2012) [21]. Despite of having such harm BPS is still widely used (Rochester and Bolden 2015) [31].

Effect of BPA and BPS on different reproductive components

In females

The effect of BPS on follicular cell function in mammals is not properly understood but, BPA affects variety of structures like granulose cells (Mansur *et al*., 2016) [24], and theca cell (Zhou *et al*., 2008) [48]. Sensitivity of oocyte maturation towards endocrine disruptor depends upon maturation media composition used invitro. Recent studies found that BPS is not detected in follicular fluid of pig collected from abattoir (Zalmanova *et al*., 2017) [46]. Because of herbivorous nature of bovine feeding, they are less likely to be exposed to EDC which have tendency to bioaccumulation in higher tropic level (Magnusson and Persson, 2015) [23] but some studies found the level of BPS similar to BPA i.e., 229-305 ng/lit (1-1.3nM) in urine of replacement cows (Zhang *et al*., 2014) [13]. Granulose cells become stimulated for steroid hormones synthesis and cell viability when exposed to 100µM BPS but no effect is shown in presence of FSH (Campen *et al*., 2018a) [7]. Estrogen production by granulose cell is affected by BPS through disrupting HPGA (Hypothalamus-pituitary-gonadal axis) as like in BPA (Xi *et al*., 2011) [42]. Interestingly Campen *et al*. (2018a) [7] in their studies found that estrogen production by granulose cells is stimulated by BPS in contrast to BPA and at the same time BPS has no effect on progesterone production from granulose cells as well as steroid synthesis from theca cells unlike in BPA (Campen *et al*., 2018a) [7], this study suggested that estrogen pathway is specific target for BPS as theca cell have negligible or absence of estrogen production by aromatic androgens in

contrast to granulose cell (Fortune and Armstrong, 1978). NMDR (non-monotonic dose response curve) type of curve is observed in endocrine disrupting chemicals (Cagarde *et al*., 2015) and in BPS also (Nadal *et al*., 2018) [26]. The unconjugated BPS shows more estrogenic activity than the conjugated one (glucuronide and sulphate) (Le Fol *et al*., 2015) [18]. BPA increases apoptotic gene expression of bovine oocyte (Saleh *et al*., 2020). Zhang *et al*. (2014) [47] concluded from his research that BPA also act by mimicking the androgen for promoting follicular growth rather than impeding it. It also causes PCOS (poly cystic ovary syndrome) in 4% of aged cattle, goat, dog and 8% women (Zhou *et al*., 2008) [48]. The estrogen and androgen agonistic and antagonistic along with thyroid antagonistic behavior shown by BPS through NMDRs phenomenon (Rubin's, 2011) [32].

Estrogen and progesterone help in development of luteal cells (Adam and Singh, 2021) [2]. Corpus luteum is major source of progesterone for ovarian cycle especially during mid-cycle and pregnancy too. Progesterone is synthesized from cholesterol precursor which, first go to mitochondria along the lipoprotein STAR (Steroidogenic acute regulatory protein), here it is converted into pregnenolone by cyt450 (CYP11A1) enzyme. This pregnenolone is then converted into progesterone in smooth endoplasmic reticulum by 3 beta –Hydroxysteroid dehydrogenase enzyme, BPA inhibits CytP450 aromatase (CYP19A1) mRNA expression (Kabakci and Yigit 2020) [15], which play crucial role in estrus cycle, and uterine contraction (Niswender, 2002) [28]. BPA and BPS both disrupt GDF9 (oocyte secreted protein) dependent expansion of cumulus cells and signaling between cumulus cell and oocyte (Acuna-Hernandez *et al*., 2018). Reem *et al*. (2021) studied that both BPA and BPS causes oocyte maturation defect by affecting expression of connexins protein but no effect on CX37 mRNA level in cumulus cell, this study depicted that BPS have effect on cumulus cell through other then CX37 protein. In mice BPA is responsible for damaging gap junctional intercellular communication (GJIC) of COCs (cumulus-oophorus complexes). BPA enters into cumulus cell through intracellular pores near connexins to prevent its ionic flow (Oh *et al*., 2015) [30].

In addition, some other studies found the effect of such pollutants on other species. BPS in zebra fish, reduces the egg production and alter the plasma estradiole concentration (Naderi *et al*., 2014) [27] but in pig it alters the hyaluronic acid production and gene expression of cumulus cell and disrupt the spindle formation and meiosis in oocyte (Zalmanova *et al*., 2017) [46]. In recent studies BPS also induces abnormalities in porcine oocyte and cumulus expression, spindle morphology, invitro rat maturation (Zalmanova *et al*., 2017) [46] and changes in aromatase inhibitor as in murine preadipocytes (Ahmed and Atlas 2016) [3] and in some cases by altering the expression of alpha and beta receptors of estrogen with 3-10 times less potency than BPA (Zalmanova *et al*., 2017) [46]. Follicular expression is also prevented in prepubertal mice by BPS (Hill *et al*., 2017) [14]. BPA decreases cleavage and blastocyst rate and changes the gene expression in bovines. Some other research represented the dis-regulating mechanism of several miRNAs (miR-21, miR-155 and miR-34c) by BPA (Sabry *et al*., 2021) [33]. BPA (lipophilic) modify cell membrane structures like protein channels and gap junctions (Lee *et al*., 2007) [19]. the number of female frogs increases at 23 µg BPA/lit of water (Talpade *et al*., 2018) [37]. 1µg BPA/lit of water effect female freshwater snail by stimulating egg production and swelling of sexual gland in snails (Oehlmann *et al*. 2000) [29]. BPA has wide spread of effects of birds like increased embryonic mortality in chicken *(Gallus domestic*) and reproductive organ defects.

In males

BPA at low and high dose responsible for sertoli cell and spermatozoa apoptosis and necrosis in goat but in dogs and cats it is responsible for prostate cancer, inefficient sexual differentiation, deteriorated sperm quality, impaired learning ability and adverse effect on offspring of even up to 3 generations. Besides these, other effects are reproduction organ defects, poor sperm quality, retarded sperm maturity and shifting of sex ratio in fishes (Talpade *et al*., 2018) [37]. There are color variations in male red shiners when swim into BPA containing water (Flint *et al*., 2012) [10]. In reptiles the BPA level of 1400 µg/lit of water (90 µg/egg) lead to abnormal seminiferous tubules and high concentration during gender determination, increase number of females (Talpade *et al*., 2018) [37]. Some other studies found delayed comb, wattle and testicle growth in male after oral dose of 2 µg BPA/1000gram bodyweight, every second day for a week (Furaya *et al*., 2003) [11]. BPA also affect other systems of body besides reproductive system such a**s** structural, neurological (hypersensitivity, learning defects, aggression and drug addiction). There are also some hormone related cancers like breast, prostate and ovarian endometrial carcinoma by BPA exposure (Gao *et al*., 2015) [12]. In the study of Ge *et al*. (2014) [13] the proteosome of Sertoli cell is down regulated by BPA, but there is no evidence of BPS with such mechanism of action.

BPA causes abnormalities in meiosis, spindle fiber and congenital defects in mice (Lenie *et al*., 2008) [20], pig (Wang *et al*., 2016) [40], cow, human (Machtinger *et al*., 2013) [22]. Some comparative studies concluded that BPS do not alter outcomes as BPA does, depends upon cell type (Boucher *et al*., 2016) [4]. The study of Campen *et al*. (2018b) [6] observed negative impact of BPA and BPS on cytoskeleton and chromosome of bovine oocyte with spindle abnormalities observed at 1 fM BPA and 10 fM BPS but chromosomal misalignment at 10 fM of BPA and BPS. BPA has no effect on oocyte at meiosis second stage (Campen *et al*., 2018b) [6]. Comparative study by Campen *et al*. (2018b) [6] concluded the greater decline in bipolar spindle in meiosis second stage of oocyte by BPS than BPA. Spindle and chromosomes are affected at very low dose of both bisphenols in non-linear fashion.

Conclusion

We are living in the world of plastic and the uncontrolled industrialization makes it impossible to avoid plastic use in daily life. The upcoming generation believing that plastic packaged material is much more protected from contamination, but is not aware of such toxicants that leach from such packaging. The plastic bottles are widely used in daily life by each and every person in the world because of ease to carry and wash. Some also repeatedly use some single use bottles. Growing world feels that plastic is beneficial for modern civilization but ignore such kind of deleterious defects in all type of living forms, Due to wide range of pollution caused by such uncontrolled entities. Industrialization has caused a very adverse and often irreversible change in human health in these modern times.

Therefore, it is time to minimize such dangerous products from daily life and shifting towards the use of natural and safe materials. Bisphenol A widely used chemical with various types of effects on variety of body functions in various living as well as non-living creatures which still wants further research. We are not totally against the use of plastic or industrialization, but there should be awareness among peoples that plastic, which is an unavoidable part of our life is source of such and many other (some are still unknown) nuisance and harmful (even fatal also) chemicals, so try to use plastics as little as possible in daily life and promote industrialization with natural harmless materials. In best of our knowledge no research till now concluded that the plastic is good for health, it just makes peoples life easier for short term satisfaction, additionally make them unhealthy for long period of time. Upcoming centuries introduced wide varies of plastics and its products with variety of chemicals so, there is serious need for more and more study and research in direction of plastic pollution and its effects on health.

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