Toxics Link
for a toxics-free world

Endocrine disruptor

REVIEW OF INDIAN RESEARCH

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About Toxics Link

Toxics Link is an Indian environmental research and advocacy organization set up in 1996, engaged in disseminating information to help strengthen the campaign against toxics pollution, provide cleaner alternatives and bring together groups and people affected by this problem.

Toxics Link's Mission Statement - "Working together for environmental justice and freedom from toxics. We have taken upon ourselves to collect and share both information about the sources and the dangers of poisons in our environment and bodies, and information about clean and sustainable alternatives for India and the rest of the world."

Toxics Link has a unique expertise in areas of hazardous, medical and municipal wastes, international waste trade, and the emerging issues of pesticides, Persistent Organic Pollutants (POPs), hazardous heavy metal contamination etc. from the environment and public health point of view. We have successfully implemented various best practices and have brought in policy changes in the afore mentioned areas apart from creating awareness among several stakeholder groups.

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Foreword

Modern human life can't be imagined without the use of chemicals, and an all pervasive notion that all chemicals aid in improving quality of human life thus driving increase in production and consumption of chemicals.. The world today uses approximately 100,000 chemicals and newer chemicals continue to be synthesized and brought into markets for use in products and processes. The world also understands that there is a significant gap between the pace of generation of new chemicals and information on its life cycle assessment and any adverse health and ecological impacts due to use of these chemicals. Endocrine Disrupting chemicals is new categorization of chemicals that are recognized for their adverse impacts on endocrine systems causing serious and long term impacts on human health and ecology. Interestingly, most new chemicals are synthesized and marketed in the developed world, the data on downside impacts also usually emanates from the global North which at times does raise some questions on impacts of these chemicals in various mediums due to stark climatic differences. However, during our engagement on EDC in India, we did meet with scientists and scholars who were actively researching and publishing new information of chemicals.

The importance and criticality of local data can never be over emphasized hence the need to collate this information in the form of a compendium. This compendium has attempted to capture most published research work on EDC from India thus providing a snapshot into the range of research undertaken and capturing a rich diversity of data which can be put to multiple use. Amazingly the body of research on EDC is significantly large and deep which also encouraged and inspired the team to bring together such a document. Toxics Link team has invested substantive efforts in bringing out this document and placing it in public domain and I do hope that this will be a great resource and of immense value to all stakeholders.

Satish Sinha

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Abbreviations

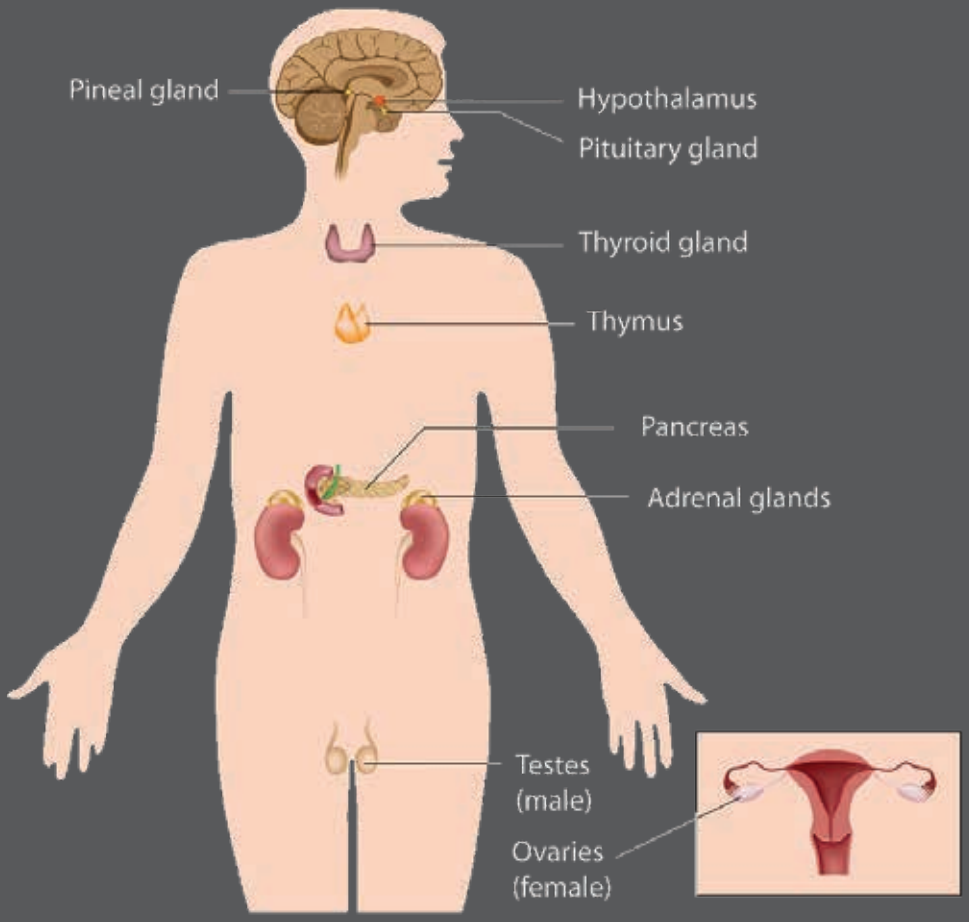
ADI	Applicability Determination Index
AR	Androgen Receptor
BAFs	Bioaccumulation Factor Based on Sediment
BAFw	Bioaccumulation Factor Based on Water
BBP	Benzyl butyl phthalate
BPA	Bisphenol A
CaBP-9K	vitamin-D-dependent calcium-binding protein
CNS	Central Nervous System
CPCB	Central Pollution Control Board
DBP	Dibutyl phthalate
DDT	Dichlorodiphenyltrichloroethane
DEHP	Bis(2-ethylhexyl) phthalate
DEHP	Di-2-ethylhexyl phthalate
DHP	Dihexyl phthalate
DIDP	Diisodecyl phthalate
DINP	Diisononyl phthalate
DNA	Deoxyribonuclic Acid
DNOP	DI-N-Octyl phthalate
DOP	Dioctyl phthalate
DVD	Digital Versatile Disc or Digital Video Disc
EDCs	Endocrine Disrupting Chemicals
ENR	Enoyl-acyl carrier-protein reductase
EO	Ethylene Oxide
EPS	Extruded Polystyrene Foam
ER	Estrogen Receptor
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration
GC-MS	Gas chromatography–Mass Spectrometry
GFP	Green Fluorescent Protein
GSI	Gonadosomatic Index
iNOS	Inducible Nitric Oxide Synthase
LC50	Lethal Concentration 50
LOD	Limits of Detection
Lux	luciferase
MBP	Monobutyl phthalate
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MEP	Monoethyl phthalate
mg/kg	Milligram per kilogram
mg/L	Milligram per Liter
ng/L	Nanogram per liter
NP	Nonylphenol
NPE	Nonylphenol Ethoxylates
NSC	Neural Stem Cell
NTP	National Toxicology Program
OP	Octylphenol
PBDE's	polybrominated diphenyl ethers
PC	Polycarbonate
PCB's	polychlorinated biphenyls
PCO	Polycystic Ovary Syndrome
PCPs	Personal Care Products
PE	Phthalate Esters
PEIs	Polyetherimides
POL	Postimplantation Loss
ppb	Parts Per Billion
PPCPs	Pharmaceuticals and Protective Care Products
ppm	Parts Per Million
PS	Polysulfone
PVC	Polyvinyl Chloride
PXR	Pregnane and Xenobiotic Receptor
RNA	Ribonuclic Acid
SAN	Styrene Acrylonitrile
SBL	Styrene-Butadiene Latex
SBR	styrene-butadiene rubber
SD	Standard Deviation
StAR	steroidogenic acute regulatory protein
TEDX	The Endocrine Disruption Exchange List
TNPP	tris (4¬nonyl¬phenyl) phosphite
US EPA	United States Environmental Protection Agency
VOC	Volatile Organic Compounds
WW	Wet Weight
WWTP	wastewater treatment plants
µg/L	Microgram per Liter

A review

This document is intended to collect information on some of the Endocrine Disrupting Chemicals (EDCs) which includes the usages of these EDCs in consumer products, its human and environmental health impacts based on the research studies carried out in Indian context and general information from secondary sources (worldwide). This document will help to spread awareness among the consumers, encourage researchers to carry out more research and bring new information in public domain and for policymakers this document will help to take appropriate actions to bring / modify regulation and sound management of these EDCs to save public and environmental health.

EDC toxic effects on children, pregnant women and elderly

The Endocrine System



Source: http://www.livescience.com/26496-endocrine-system.html

About Endocrine Disrupting Chemicals

Endocrine disruptors are the chemicals generally known to interfere with hormone action by altering the endocrine system thus having adverse impact on the human beings and other fauna including wild life.

A wide variety of chemicals act as endocrine disruptors. The Endocrine Disruption Exchange List (TEDX)[1] has listed many chemicals as endocrine disruptors till date. Chemicals commonly detected in products include bisphenol A (BPA), Triclosan (TCS), Triclocarban, paraben, nonylphenol, polychlorinated biphenyls (PCB's), polybrominated diphenyl ethers (PBDE's), and a variety of phthalates.

Endocrine-disrupting chemicals (EDCs) have attracted special attention due to its reported toxic effects on children, pregnant woman and elderly.[2,3] The issues of EDCs have been a global issue and the countries across the globe are trying to phase out these chemicals from the products as far as possible.

- A study conducted by professor **Tyagi** (2003)[4] suggests that although a number of screening methods being used for identifying potential endocrine disruptors have generated a wealth of information, a search for alternative combination of methods is still needed to overcome experimental artefacts. There are generally no accepted or validated screening methods for monitoring and studying impact of environmental endocrine disruptors. Also, no single assay can accurately predict all the deleterious effects of endocrine disruptors. For this reason various environmental protection agencies, mainly European and US, have urged that a battery of tests in current use need to be designed to assess their adequacy in detecting the effects of endocrine disruptors.
- **Nagendra Kumar Chaturvedi**, et al. in 2010,[5] conducted a study on systematic comparison of the impact of some potential endocrine disruptors (EDs) which were DDT, BCH, Chlozolinate, Nitrofen, Procymidone, Metribuzin, and ten more on modulation of androgen receptor (AR) and pregnane and xenobiotic receptor (PXR) function in a multi-step analysis. In its study the promoter–reporter-based transcription assays were performed in conjunction with receptor dynamic studies in living cells which helped implicating the suspected EDs for their deleterious effects. It has demonstrated that most of the selected EDs not only inhibit AR transcriptional activity, but also alter its subcellular dynamics. Conversely, some of these anti-androgenic compounds were potent activator of xeno-sensing nuclear

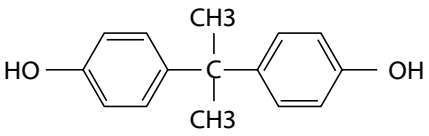
receptor, PXR. Interestingly, agonist-activated AR that associates with the mitotic chromatin fails to achieve this association when bound to anti-androgenic EDs. Conclusively, most EDs (except BCH) behaved like pure antagonist for AR while as agonist for PXR. Subsequent experiments with DDT treatment in mice model indicated that in testis AR and its regulated genes PEM and ODC levels are down-regulated, whereas in liver of same mice PEM is up-regulated while AR and ODC remain unchanged.

- A review study done by **Gargi Bagchi Bhattacharjee**, et al. in 2014[6] expressed that the Endocrine disruptive chemicals (EDCs) modulate hormone signaling and causing developmental and reproductive anomalies. Now a days, there is a global concern regarding endocrine disruption effects, particularly those mediated by the androgen receptor (AR). Androgen or male hormones are critical for the development and maintenance of male characteristics and numerous EDCs exist in the environment with the potential to disrupt androgen action. The threat is more during critical developmental windows when there is an increased sensitivity to these compounds. Timely screening and detection of EDCs is essential to minimize deleterious effects produced by these toxic chemicals. As a first line of screening, in vitro transcription assays are very useful due to their speed, convenience, and cost effectiveness. In their research, recent in vitro reporter assays for detecting androgenic or antiandrogenic activity of EDCs have been reviewed. Two important cell systems used for this purpose, namely, the mammalian or yeast cell systems, have been discussed. Use of reporter genes such as bacterial luciferase (lux) and green fluorescent protein (gfp) has significantly improved speed and sensitivity of detection. Also, many of the current reporter assay systems can be used in a high throughput format allowing speedy evaluation of multiple potential EDCs at a lower price.

Potential Endocrine Disrupting Chemicals

1. Bisphenol A (BPA)
2. Triclosan
3. Triclocarban
4. Phthalates
5. Parabens
6. Nonylphenol
7. Di-ethanolamine
8. Styrene

1. Bisphenol A (BPA)



Bisphenol A (BPA) is a carbon-based synthetic compound with the chemical formula (CH3)2C(C6H4 OH)2 belonging to the group of diphenylmethane derivatives and bisphenols. The commercial use of BPA started in 1957. BPA is primarily used as a monomer in the manufacturing of polycarbonates, a high performance transparent, rigid plastic. BPA is also used in flame retardants, unsaturated polyester resins, polysulfone (PS) resins and poly-etherimides resins, polysulfone (PS) resins and polyetherimides (PEIs). BPA is a chemical that has been used to harden plastics for more than 40 years; it has the potential to leach in small amounts into food and beverages stored in materials containing these substances. Human beings are exposed to BPA through their diet, inhalation of household dust, and dermal exposure. BPA is a well known endocrine disruptor.

Usages

Consumer Products

Bisphenol A is widely used in the production of plastic products (polycarbonates, epoxy resins), flame retardants, thermal papers etc. BPA-based products also include DVDs, computers, home appliances, spectacles and optical lenses, reusable water bottles, food storage containers, sports safety equipments, medical equipments, construction material, paints and coatings.

Products meant for Children

Baby feeding bottles, Sippy cups, teethers, baby formula cans etc.

Research studies on BPA content in various products

- **Saxena** et al. (2013)[7] detected BPA up to 46.05 ppb in the water used for sterilization of baby bottles. BPA contamination may occur from many different sources, but the most common way of BPA contamination in children is through packaged foods or beverages where the packaging material contains BPA. The children also use the container made of PC plastics are favored for their sturdiness, light weight, shatter resistance, durability, optical clarity, heat tolerance, etc. For these reasons, most of the products including children products like feeding bottles are made with such plastics using BPA. However, the additive, BPA gets liberated from the food container, at particular environmental conditions and contaminates the food stuff stored.
- It has been reported that the acidity or alkalinity of food, mode of cooking/heating, temperature of food during storage, nature of

Research studies have found that children are most susceptible to the impact of BPA.

cleaning detergents and age of the container are factors governing BPA migration.[8,9,10,11,12] In 2014 a study conducted by Shrinithivihahshini et al. revealed the Bisphenol A migration study in baby feeding bottles of selected brands available in the Indian market.[13] They have tested the safety of using PC bottles, for feeding infants with respect to BPA and the migration rate of BPA from the containers, while storing hot water at 70^{0}C, for 1 h. Three different popular brands of PC baby feeding bottles were subjected to the tests.

The study reveals that the PC baby feeding bottles available in the Indian market are likely to leach around 19ng of BPA ml^{-1} of milk. According to the European commission's Scientific Committee on Food, an infant of 4.5 kg could consume about 700 ml of milk per day[14] if the present BPA migration level of 19 ng ml exists, an infant by feeding through such PC bottle is likely to get 2.9 µg of BPA d^{-1} kg^{-1} of its body weight. It can be argued that the container may not leach the same amount of BPA every time. But there are evidences for continuous and enhanced level of BPA migration due to the effect of temperature, pH of food and age of the container.

Other than this there are many studies which focus on the effect of BPA on the reproductive health in animals, there are no precise studies on the impact of BPA on human health.

Bisphenol A and human health

Impacts on Children

The epidemiological studies found correlations between BPA exposure and heart diseases, liver toxicity and metabolic syndrome (diabetes obesity).[15] Researchers have reported that exposure to low doses of BPA lead to disruptive effects in androgen or estrogen responsive tissues, within the immune system, the thyroid, and the developing nervous system.[16,17]

Due to the structural similarity of BPA with 17 β estradiol, the former compound binds with the estrogen receptor (ER) and alters its functions.[18,19,20] Hence continuous use of such plastic containers for food preparation and storage is likely to add up the body burden to a level that causes hormone-related problems; the impacts of BPA chemical residues on endocrine system vary with the dosage, body weight and synergistic actions of hormones.

Impacts on Women

Bisphenol–A has varied impact on women health. A higher BPA levels were linked to a reduced number of follicles and therefore fewer fertile eggs.[21] Due to its phenolic structure, BPA has been shown to interact with estrogen receptors and to act as agonist or antagonist via estrogen receptor (ER) dependent signaling pathways. Therefore, BPA has been shown to play a role in the pathogenesis of several endocrine disorders including female and male infertility, precocious puberty, hormone dependent tumours such as breast and prostate cancer and several metabolic disorders including polycystic ovary syndrome (PCOS).[22]

Researchers have also revealed that BPA can be found in both the placenta and the amniotic fluid of pregnant women. So when a pregnant woman is exposed, thereby the fetus has the possibility of BPA exposure. BPA can be found in breast milk also.[23] There are no specific studies observed on the impact of BPA on human being in Indian context.

Bisphenol A and Environment (Air, Water and Soil)

BPA can enter the environment either directly from chemicals, plastics, coat and staining manufacturers, from paper or material recycling companies, foundries who use bisphenol A in casting sand, or indirectly leaching from plastic, paper and metal waste in landfills or ocean-borne plastic trash. Ubiquity makes BPA an important soil pollutant. BPA can currently also be found in municipal waste water. It affects growth and development in aquatic organisms. Among freshwater organisms, fish appear to be the most sensitive species followed by aquatic invertebrates, amphibians, and reptiles. In addition, BPA affects reproduction in aquatic and terrestrial annelids, molluscs, insects, crustaceans, fish and amphibians; impairs development in crustaceans and amphibians and induces genetic aberrations.[24,25]

Bisphenol A and Animals

- BPA acts as an endocrine disruptor to fish and adversely affect the reproductive physiology, gonadal development and function of the fish was clearly exhibited in the study done by **Manisha Sisodiya** et al 2017.[26] Furthermore, the researcher observed the relationship between BPA and the reduction of Gonadosomatic Index (GSI). The outcome of this study showed the significant decrease in fecundity and pathological symptoms in all experimental groups than in the control group. These findings were reasonably indicators of reproductive impairments leading to delayed gonadal maturity and negatively affecting processes of ovulation and thus, the fish production.
- A study conducted by **Tushara Vijaykumar** et al in 2017[27] observed ultrastructural changes caused by BPA in testicular morphology and this might be an indication of a perturbed sperm production. Considering the genetic and spermatogenic similarities of common marmoset (Callithrix jacchus).
- In a study done by **Swati Agarwal**, et al in 2016 noted, many changes in the rat brain. From the experimental results, it has been concluded that BPA induced neurotoxicity was corroborated with impaired autophagy and mitochondrial dynamics. BPA mediated impaired mitochondrial dynamics was associated with inhibition of neural stem cell (NSC) proliferation and differentiation. Researcher suggested that however, the effects of BPA on impaired mitochondrial dynamics need to be further in depth explored in context with the overall mitochondrial biogenesis and mitochondrial protein import in the brain.[28]
- The effects of BPA have been documented in various previous studies using short term exposure and by injecting directly, a similar observation was also recorded by **Priya Gupta** and **Seema Srivastava** in their "Bisphenol A: Cause of Male Infertility" research study (2015).[29] The aim of their study was to evaluate the effect of bisphenol A (BPA), a contaminant of resin-based dental composites and sealants, on the fertility of male adult wistar albino rats. Adult male albino rats of strain weighing approx. 150-200gm were divided into four groups of 10 each. BPA (5, 50 and 100 µg /100gm/bw) was administered orally daily to the rats in the test groups and olive oil to the control group for 90 days. Male fertility was assessed periodically by mating each rat with two untreated females. There were significant reductions in the absolute weights of the testes and disrupted spermatogenesis was observed at 50 and 100µg dose level of BPA whereas at 5 µg dose level did not show any such significant effect. Epididymal epithelium degeneration was observed at 5, 50 and100µg dose level. Cauda sperms were found to be reduced in the 100µg dose treated animals. Reduction in the serum testosterone was also observed in treated animals. Study concludes that BPA affects reproduction with impaired fertility in male rats.
- In 2014 **Chouhan** et al. carried out a study to investigate the mode of BPA's action by evaluating its effect on the expression of inducible nitric oxide synthase (iNOS) and steroidogenic acute regulatory protein (StAR) in male mice testis.[30] In their study the Swiss albino mice were treated with range BPA concentrations of 0.5, 50 and 100 µg/kg body weight/day intraperitonially for 60 days. Several markers of oxidative stress and male fertility were investigated. Nitrite levels, malondialdehyde levels and testicular injury scores were elevated whereas the sperm count, serum testosterone levels and catalase activity were reduced in the BPA groups. Mechanistically, an increase in iNOS expression was observed in the testis whereas the expression of the StAR was down regulated in the BPA treated mouse. These results suggest that BPA induces oxidative stress by altering the expression of iNOS, which consequently leads to the down regulation of StAR expression in the testis of male mouse.
- Sperm count is an important parameter to analyze toxic effects of any substance on male reproduction. The result obtained from the study done by **Shikha Chouhan** et al. in 2013 suggested that BPA caused a significant reduction in sperm production in male mice and steroidogenesis in male testis. An impaired histological architecture and a reduced testosterone level in BPA exposed mice gives a clear picture of impaired activity of Leydig cells. Thus the results obtained in the study clearly demonstrated that long term BPA exposure to male mice at low dosed was capable of adversely affecting the male fertility by causing severe damages to the spermatogenesis and steroidogenesis process.[31]

- A similar study done by **Sharma** and **Kalita** in 2013 evaluated the estrogenic effects of Bisphenol-A and Octylphenol in reproductive health of male albino mice. The albino mice of equal weights were taken into five groups. Group-I mice were left untreated, group-II treated with vehicle control, group-III treated with Octylphenol and group-IV treated with Bisphenol-A both with the amount of 80mg/day/kg body weight and group-V treated with 17-ß estradiol in amount of 120µg/kg/day. These compounds were administered subcutaneously in a volume of 100µl for seven consecutive days. Significant decrease in the weight of Testis, Epididymes and Sperm count were observed in the mice treated with the two industrial chemicals and the noted effects were similar with that of 17-ß Estradiol. The results showed estrogenic property of Bisphenol-A and Octylphenol.[32] Both BPA and OP act like estradiol but their potency was lower than that of endogenous estrogen, 17 ß estrodiol. Both these chemicals had reduced the weight of testes and epididymes. Exposure to BPA and OP resulted in decrease in sperm count in epididymal fluid.

BPA caused a significant reduction in sperm production in male mice and steroidogenesis in male testis

- **Jayanti Pant** and **Shripad B. Deshpande** (2012) did a study on acute toxicity of Bisphenol A in rats. The study was undertaken to determine the median lethal dose (LD50) of BPA via intraperitoneal (ip) and intravenous (iv) route in adult rats (by Dixon's up and down method) and also to know the acute systemic changes (in blood pressure, respiration and ECG) produced by lethal dose of BPA. Adult female albino rats of Charles Foster strain were used in the study. LD50 of BPA was 841 and 35.26 mg/kg body weight for ip and iv- route, respectively. Injection of lethal dose of BPA (40 mg/kg body weight) produced acute toxicity manifesting as immediate respiratory arrest and hypotension after the injection of BPA followed by bradycardia. The animals died within 7.3 +/- 0.7 min. Volume of ethanol (vehicle; 0.1 mL) present in the lethal dose of BPA was not lethal and had no effect on respiration, blood pressure and heart rate.
- A study done by **Tanvi Doshi** et al in 2012 documents that neonatal exposure of male rats to BPA might have altered the sperm epigenome, thereby leading to decreased expression of Dnmts and related transcription factors in the embryo, also affecting the embryo development and resulting in an increased frequency of postimplantation loss (POL) ultimately leading to subfertility.[33] Similarly **Tanvi Doshi** et al in 2011 studied Hypermethylation of estrogen receptor promoter region in adult testis of rats exposed neonatally to bisphenol A and suggested the need of toxicological assessment of endocrine disruptors at epigenetic level and analysis of genome wide DNA methylation pattern to be taken into consideration for risk assessment.[34]
- **Salian S**. et al in 2009 did a study on the effect of Bisphenola A rats and claimed that the study demonstrates for the first time that the exposure of rats to environmentally relevant doses of BPA during the perinatal period leads to impairments in fertility and perturbations in the testicular steroid receptors expression pattern in female offspring and their subsequent generations. The transgenerational effects observed in the present study are mediated via germ line transmission.[35]

It has been found that BPA has the potential to have a wide range of health effects on humans and other organisms, especially involving reproductive health. There is still a lot of research to be done to determine what levels of BPA are safe for adults, children, and animals as well as the environment. Research also needs to be done on how to best detect and remove BPA from everyday products, especially related to food packaging and preparation. Lastly, it is important to find the best method to remove BPA from the environment.

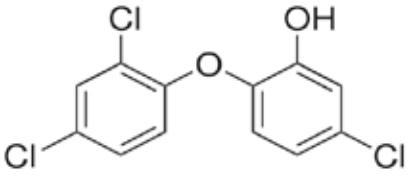
It is being used as a monomer in the manufacturing process of polycarbonate plastics for consumer products (e.g. baby feeding bottles, sippy cups, etc) and epoxy resin linings for food and beverage containers and for polyacrylate dental materials. There are more products in which BPA used viz., carbonless paper (thermal paper) and plastic toys.[36,37]

TABLE 1: COMPILED RESEARCH STUDIES ON BPA WITH IMPORTANT FINDINGS

Year	Author	Location	Title	Important Findings
2013	**Johnson S, Saxena P, Sahu R**	New Delhi	*Leaching of Bisphenol A from baby bottles*	Detected BPA up to 46.05 ppb in the water used for sterilization of baby bottles.
2014	**D. Shrinithivihahshini, D. Mahamuni and N. Praveen**	Tiruchirappalli	*A migration study in baby feeding bottles of selected brands available in the Indian market*	PC baby feeding bottles available in the Indian market are likely to leach around 19ng of BPA ml–1
2017	**Manisha Sisodiya, Meena Khare, R.R. Kanhere**	Jhabua (MP)	*Endocrine disrupting effects of BPA on reproductive physiology of female fish heteropneustes fossilis*	BPA acts as an endocrine disruptor to fish and adversely affect the reproductive physiology, gonadal development and function of the fish was clearly exhibited in the study. The researcher observed the relationship between BPA and the reduction of Gonadosomatic Index (GSI).
2017	**Tushara Vijaykumar, Dipty Singh, Geeta R. Vanage, Rohit V. Dhumal & Vikas D. Dighe**	Mumbai	*Bisphenol A-induced ultrastructural changes in the testes of common marmoset*	Observed ultrastructural changes caused by BPA in testicular morphology and this might be an indication of a perturbed sperm production. Considering the genetic and spermatogenic similarities of common marmoset (Callithrix jacchus).
2016	**Swati Agarwal, Anuradha Yadav, Shashi Kant Tiwari, Brashket Seth, Lalit Kumar Singh Chauhan, Puneet Khare, Ratan Singh Ray, Rajnish Kumar Chaturvedi**	Lucknow	*Dynamin-related protein 1 inhibition mitigates Bisphenol-A mediated alterations in mitochondrial dynamics and neural stem cells proliferation and differentiation*	BPA induced neurotoxicity was corroborated with impaired autophagy and mitochondrial dynamics. BPA mediated impaired mitochondrial dynamics was associated with inhibition of neural stem cell (NSC) proliferation and differentiation
2015	**Priya Gupta and Seema Srivastava**	Jaipur	*Bisphenol A: Cause of Male Infertility*	BPA affects reproduction with impaired fertility in male rats.

Year	Author	Location	Title	Important Findings
2014	**Chouhan, S., Yadav, S.K., Prakash, J., Westfall, S., Ghosh, A., Agarwal, N.K., Singh, S.P.**	Varanasi	*Increase in the expression of inducible nitric oxide synthase on exposure to Bisphenol A: A possible cause for decline in steroidogenesis in male mice*	BPA induces oxidative stress by altering the expression of iNOS, which consequently leads to the down regulation of StAR expression in the testis of male mouse.
2013	**Shikha Chouhan, Jay Prakash, Satyndra K Yadav, Neeraj K Agrawal**	Varanasi	*Effect of Bisphenol A on Fertility of Male Mice*	that long term BPA exposure to male mice at low dosed was capable of adversely affecting the male fertility by causing severe damages to the spermatogenesis and steroidogenesis process
2013	**P Sharma and J.C.Kalita**	Guwahati	*Estrogenic Effects of Bisphenol-A and Octylphenol on Reproductive Health of Male Albino mice*	Exposure to BPA and OP resulted in decrease in sperm count in epididymal fluid.
2012	**Tanvi Doshi, Criselle D'Souza, Vikas Dighe, and Geeta Vanage**	Mumbai	*Effect of Neonatal Exposure on Male Rats to Bisphenol, A on the Expression of DNA Methylation Machinery in the Postimplantation Embryo*	Neonatal exposure of male rats to BPA might have altered the sperm epigenome
2012	**Jayanti Pant, Shripad B. Deshpande**	Banaras Hindu University, Varanasi	*Acute Toxicity of Bisphenol A in Rats*	The results provide evidence that the acute exposure to BPA produces lethality with a very narrow range of lethal and survival dose for iv route. Further, the lethality appears to be due to respiratory arrest and hypotension.
2011	**Tanvi Doshi, Criselle D'Souza, Vikas Dighe, and Geeta Vanage**	ICMR-National Institute for Research in Reproductive Health, Mumbai, Maharashtra	*Effect of Neonatal Exposure on Male Rats to Bisphenol, A on the Expression of DNA Methylation Machinery in the Postimplantation Embryo*	The study suggested the need of toxicological assessment of endocrine disruptors at epigenetic level and analysis of genome wide DNA methylation pattern to be taken into consideration for risk assessment
2009	**Salian S, Doshi T, Vanage G**	Mumbai	*Perinatal exposure of rats to Bisphenol A affects the fertility of male offspring*	The transgenerational effects observed

2. Triclosan



The chemical Triclosan was introduced in 1972 for use as a surgical scrub in hospitals. Since then, it has increasingly been added to a wide variety of products.[38] It's a phenylether, or chlorinated bisphenol with a broad-spectrum antimicrobial action which is classified as a Class III drug by the FDA (Class III drugs are compounds with high solubility and low permeability).[39] Triclosan is a synthetic, broad-spectrum antimicrobial agent that in recent years has exploded onto the consumer market in a wide range of products.[40] Triclosan is incorporated in cosmetics mainly as a preservative, to stop bacteria from growing on the product and spoiling it. It is also used as a biocide in many other personal care products such as deodorants, soaps and shower gels. Triclosan is used in biocidal products for veterinary hygiene and not as a preservative in animal food.[41]

Usages

Consumer Products

- Toothpastes
- Antiseptic soaps
- Mouthwash
- Deodorant
- Hair products
- Detergents

Products meant for women

- Cosmetics

Triclosan and Human Health

The uses of Triclosan are linked to the following effects on human health:

- Abnormal endocrine system/thyroid hormone signaling.
- Weakening of immune system.
- Children exposed to antibacterial products at an early age have an increased chance of developing allergies, asthma and eczema.
- Uncontrolled cell growth.
- Developmental and reproductive toxicity.

Triclosan is a well-known chemical for its endocrine disrupting properties. Triclosan is lipophilic in nature, so the chemical generally binds and bioaccumulate in the fatty tissues. As it is very commonly used in the personal care products, it can penetrate into the skin and has the tendency to interfere with harmonal functions. It may impact male and female hormones like testosterone and estrogen, and may also affect thyroid systems, which regulate weight and metabolism.[42,43,44]

Studies have increasingly linked Triclosan (and Triclocarban), to a

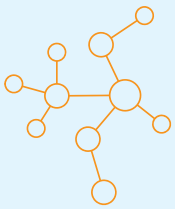
range of adverse health and environmental effects from skin irritation, endocrine disruption, bacterial and compounded antibiotic resistance, to the contamination of water and its negative impact on fragile aquatic ecosystems. Triclosan is similar in its uses and mechanism of action to Triclocarban.[45]

Triclosan and Environment (Air, Water, Soil and Crop)

- The Triclosan is one of the most frequently detected compounds in the sewage analysis and is found to reveal toxic effects on aquatic organisms.[46,47] The release of Triclosan into aquatic systems causes adverse effects on the environment and biota and aquatic flora.[48,49] Triclosan is toxic to aquatic bacteria at levels found in the environment. It is highly toxic to various types of algae and has the potential to affect the structure of algal communities, particularly immediately downstream of effluents from wastewater treatment facilities that treat household wastewaters. Triclosan has been observed in multiple organisms, including algae, aquatic black worms, fish, and dolphins. It has also been found in land animals including earthworms and species higher up the food chain. Triclosan favors anaerobic conditions which is typical in soil and sediment. The antimicrobial properties of Triclosan are resistant to anaerobic degradation which is the main contributor to its persistence in the environment.[50,51]
- In 2016 **Bharadwaj**, et al studied the effect of Triclosan on the germination and seedling growth of mustard seed. For this study, they have collected the sewage samples from the inlet of Sewage Treatment Plant, Karnal and after filtration this water was used in the germination of different mustard seeds, seeds germinated with distilled water was kept as a control. It was observed that the germination assessment of different plant species in distilled and sewage revealed unexpected results, which showed that 87% germination in control condition while in sewage significantly decreased germination percentage by 58 % and Triclosan reduced germination percentage by 96%). This study further demonstrated that application of Triclosan treatment increase some important traits of mustard seeds in germination and seedling growth. Percentage of germination, viability, number of roots, shoot and root length, fresh weight, and dry weight of the rice seedlings showed an inverse relationship with the effluent concentration.[52]

Triclosan and Animals

- A study done by **Ravi Kumar Kola**, et al., in 2015 investigated the aquatic toxicity of Triclosan by studying the total protein content modifications in fish, Channa punctatus. The experimental fishes were divided into four groups a) control, b) low (0.1 ppm), c) medium (0.5 ppm) and d) high (1.0 ppm) concentrations and they were exposed to technical grade Triclosan for 96 hrs. The live fishes were sacrificed after 96 hrs and total protein content was analyzed from five different tissues viz., brain, liver, kidney, gill and muscle. The total protein content was maximum in liver with depletion of 31.64% in 0.1 ppm, 46.39% in 0.5 ppm and 64.36% in 1.0 ppm, compared to control. The total protein content was minimum in brain with depletion of 18.20% in 0.1 ppm, 39.92% in 0.5 ppm and 59.11% in 1.0 ppm, compared to control. The decrease of total protein content may be due to enhanced proteolytic activity and decreased anabolic activity of protein under stress condition towards Triclosan. The results suggested that Triclosan causes hazardous effects to aquatic organisms especially fishes even at lower concentrations. The effects of these deleterious chemical goes unnoticed because most of the changes occurring in the body of the fish were minute and if the indiscriminate usage of Triclosan continues it will become irreparable when it gets accumulated and spread through aquatic and terrestrial food webs.[53]
- In an another study by **Govindaraj Shanmugam**, et al., in 2014,[54] studied the Triclosan in fresh water fish Gibelion Catla from the Kaveri River, India,



The decrease of total protein content may be due to enhanced proteolytic activity and decreased anabolic activity of protein under stress condition towards Triclosan

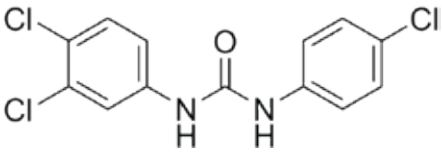
and its consumption risk assessment, In their study, Triclosan was quantified in fish by using the gas chromatography and mass spectrometry technique and it was found in the range of 0.73–50 ng/g wet weight (ww). The mean bioaccumulation factor based on water (BAFw 820) and sediment (BAFs 2.12) in the Kaveri River showed that Triclosan was accumulated in fish, and reflects its feeding behavior. The bioaccumulation indicates Triclosan persistence or prevalence throughout the river stretch. This investigation is the first to report the bioaccumulation of Triclosan in freshwater fish from India. Further, the results indicate that this fish acts as a biomarker of exposure for Triclosan and thus shall be used to report Triclosan pollution in the future.

This study has successfully determined Triclosan residues in fish muscle tissue using GC/MS. Hence the method may also be applied for aquatic (farm) products quality control and also biomonitoring studies of emerging contaminants. The anthropogenic influence was recorded/ reflected in fish and also expected to continue in aquatic food chain. The human dietary exposure of Triclosan was considered safe (as per ADI and US EPA guideline), however it's in vivo activity may be influenced by co-contaminants. Being the first investigation to report bioaccumulation of Triclosan in Indian freshwater fish, the results highlight the need for further monitoring and assessment at spatial and temporal means. Further the authors suggested that the baseline data collected in the study was a starting point for Pharmaceuticals and Protective Care Products (PPCPs) forensic investigations in Indian riverine environment and it will provide clues about the past contamination events.

TABLE 2: COMPILED RESEARCH STUDIES ON TRICLOSAN WITH IMPORTANT FINDINGS

Year	Author	Location	Title	Important Findings
2014	**Govindaraj Shanmugam, Karthik Ramasamy, Krishna Kumar Selvaraj, Srimurali Sampath, and Babu Rajendran Ramaswamy**	Tiruchirappalli	*Triclosan in Fresh Water Fish Gibelion Catla from the Kaveri River, India, and Its Consumption Risk Assessment*	This investigation is the first to report the bioaccumulation of Triclosan in freshwater fish from India. Further, the results indicate that this fish acts as a biomarker of exposure for Triclosan and thus shall be used to report Triclosan pollution in the future.
2015	**Ravi Kumar Kola, Abdul Rasheed Mohd and Prameela Devi Yalavarthy**	Warangal	*Effect of Triclosan on total protein content in fresh water fish, Channa Punctatus*	Triclosan causes hazardous effects to aquatic organisms especially fishes even at lower concentrations
2016	**Rakesh Kumar Bhardwaja, Vibha Bhardwaj**	Karnal	*Effect of triclosan on germination and seedling growth of mustard seeds*	This study further demonstrated that application of Triclosan treatment increase some important traits of mustard seeds in germination and seedling growth

3. Triclocarban



Triclocarban is an antibacterial active ingredient used in wide range of personal care products like soaps, deodorants, detergents, cleansing lotions, and wipes as well as in the medical field, for which it was originally developed.[55] Triclocarban is also used globally as an antimicrobial active ingredient in bar soaps. Triclocarban in consumer antimicrobial products was designed to reduce the number of harmful bacteria on the skin better than the use of plain soap. The use of Triclocarban helps to stop the transmission of germs to other people or to objects.[56] Studies on its antibacterial qualities and mechanisms are growing. Research suggests that it is similar in its mechanism to Triclosan and is effective in fighting infections by targeting the growth of bacteria such as *Staphylococcus aureus*.[57]

Mode of Action

Triclocarban is a limited spectrum antibacterial agent, meaning that it is not effective against all microbes. There is a specific set of organisms for which Triclocarban effectively prevents or controls growth. It is insoluble in water, but is fat-soluble. It disables the activity of the enzyme called ENR (enoyl-acyl carrier-protein reductase) which humans do not have, making it harmless to humans. This enzyme is vital to building cell membranes of many bacteria and fungi.[58]

Usages

Products meant for women

- Personal Care Products (soaps, lotions, deodorants and sprays, toothpaste, roll-ons and sticks, shampoos, shaving creams, etc.) and plastics

Triclocarban and Human Health

Triclocarban prevents or retards bacterial growth, and thus protects cosmetics and personal care products from spoilage. It also reduces or eliminates unpleasant odor and protects against the formation of such odors on the skin.[59]

Animal studies have shown both the chemicals, Triclosan and Triclocarban, can interfere with hormones critical for normal development and function of the brain and reproductive system. Triclosan has been associated with lower levels of thyroid hormone and testosterone, which could result in altered behaviour, learning disabilities, or infertility. Triclocarban has been shown artificially to amplify the effects of sex hormones such as estrogen and testosterone, which could promote the growth of breast and prostate cancer. Furthermore, laboratory studies suggest that Triclosan and Triclocarban may

be contributing to antibiotic resistance in bacteria known to cause human infections.[60] Triclocarban is commonly used (together with Triclosan) as an antifungal and antibacterial agent. Although relatively little data exists about the toxicity of TCC.[61]

About 40% of soaps use at least one of these chemicals

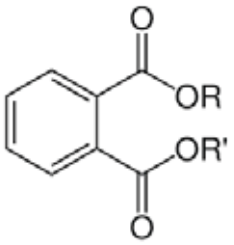
Triclocarban and Environment (Air, Water and Soil)

Extensive usage and continuous release of personal care products (PCPs) lead to ubiquitous contamination of aquatic environment. As PCPs are mainly intended for external use on the human body, they are not subjected to metabolic alterations; therefore, large quantities enter the environment. Being biologically active and persistent, they are expected to pose a wide range of risks to aquatic habitat. Although studies on environmental concentration and toxicity endpoints are available for many PCPs, environmental risk assessment (ERA) was scantily reported. It was observed that most of the ERAs were based on hazard/risk quotient approach and not following three-tier approach due to lack of sufficient toxicological data (i.e., long-term toxicity at environmentally relevant (ppt–ppb) concentrations). From the ERA reports, it was understood that disinfectants, Triclosan and Triclocarban, cause high risk to aquatic organisms.[62]

Note – there are no studies found in India which can correlate with Triclocarban with human health impacts or environmental impacts

4. Phthalates

Phthalates are a group of chemicals used to make plastics more flexible and harder to break. They are often called plasticizers. Some phthalates are used as solvents (dissolving agents) for other materials.[63] Colorless, odorless phthalates are not only cost effective, but also highly suitable for many flexible vinyl products. Some of their key characteristics include: durability, flexibility, weather resistance and ability to withstand high temperatures.[64]



They show low water solubility, high oil solubility, high octanol-to-water partition coefficient and low volatility. Phthalates are easily released into the packed food because there is no covalent bond between the phthalates and plastics in which they are mixed. Phthalates may cause major ill effects like endocrine disruption, asthma and cancer. It's a family of industrial chemicals used to soften PVC plastic and as solvents in cosmetics and other consumer products, can damage the liver, kidneys, lungs, and reproductive system — particularly the developing testes — according to animal studies.[65]

- Recently **Srinivasan** et al 2016[66] did a study on sambar, tea and alcohol, the samples were collected from different business centers around Thanjavur. The tea and sambar packed in their routinely using poylthene cover in hot condition was collected from the tea shop and restaurant. The alcohol with plastic cups which they are regularly using for consumption was collected from a beverage shop. The qualitative analysis for the presence of phthalates was performed on GC-MS chromatograph of the hexane extracts of sambar, tea and alcohol by comparing the retention times and the mass spectra registered for the compounds corresponding to the particular peaks with the mass spectra found in reference libraries. The study reveals the fact that the phthalates are highly soluble in oily food products. The Indian dish sambar is made up of various ingredients including oil. Authors further concluded that, the phthalate leached in sambar emphasized the potential danger which threatens public health and the future generation.

Usages

Consumer Products

- Food production and storage containers (such as conveyer belts, jar lids, tubing, gloves, and packaging).
- Flexible, Durable and Resistant Products
- Flexible PVC
- Building and Construction

- Wire and Cable
- Automobiles (lubricating oils, automotive plastics)
- Vinyl flooring
- Adhesives
- Plastic clothes (raincoats)
- Plastic packaging film and sheets
- Garden hoses
- In medical (Blood-storage containers, Medical tubing) etc.

Products meant for Children

- Toys

Products meant for women

- Beauty and skin care products (such as shampoos, lotions, makeup, and perfume) and in fragrances used in these products
- Plastic medical devices (IV tubing, IV fluid/total parenteral nutrition bags, catheters).

Phthalates and Human Health

Health impacts in general

DEHP: Exposure to it causes asthma and allergy in children. Studies have shown that it interferes with development of reproductive organs; exposure during pregnancy is linked to pre-term birth.

DBP: Linked to poor semen quality in men, premature breast development in women and asthma and allergic symptoms in children.

BBP: Linked to embryo toxicity, asthma and liver problems.

DINP: Linked to pre-natal toxicity, slightly increased rates of skeletal retardation, soft tissue and skeletal malformation, increased liver and kidney weight.

DIDP: Repeated exposure damages the liver.

DNOP: Causes low, acute eye and skin irritation, toxic to the liver, thyroid glands, kidney and reproductive system, Found to promote tumour formation in the liver.

- According to Krishna Kumar Selvaraj et al (2016), their research study is the first study reporting phthalates migration in packed commodities from a developing country, India, which further warrants extensive phthalates exposure assessment to understand its effect on public health.[67]
- In its studies health outcome section, **Rastogi** et al., (2006) mentioned that the human studies are scaring, but suggestive, as frequently reporting an association between phthalate exposure and health risks. The presence of phthalate metabolites in human body fluids does not by itself mean that phthalates cause disease. The adverse health effects of phthalate exposure on human population are most likely associated with the everyday use of consumer products that commonly contain a variety of phthalates like DEP, MEP, MBP etc.[68]

0.1% to 16.2%
Soft toys contain higher levels of phthalataes

Impact on children

- Potential phthalate exposure has been associated with respiratory symptoms and disease in young children.
- In 2011 **Sapna** et al[69] analyzed children toys and child care articles for eight phthalates, these samples were collected from local Indian market. All toy samples showed the presence of one or more phthalates including di-(2-ethylhexyl) phthalate (96% of the samples), di-iso-nonyl phthalate and di-iso-decyl phthalate (42% of the samples) at a concentration ranging from 0.1% to 16.2%. Soft toys contain higher levels of phthalates as compared to hard toys as primary function of phthalates is softening of hard plastic materiel. The soft toys were contained higher levels of phthalates as compared to hard toys like rattles. Young children suck and chew the toys containing phthalates may be at a higher risk of adverse effects of phthalates because of anticipated higher exposures during period of developmental and physiological immaturity as they may extract and ingest certain quantities of it.

Impacts on women

- Phthalates and their metabolites have been found potentially harmful for human and environment due to their hepatotoxic, teratogenic, and carcinogenic characteristics. There is a high possibility of dermal absorption of Phthalates via the skin. Higher possibility of exposure can occur from cosmetics that are left on skin for extended period of time. Topical exposure to Phthalate esters in cosmetic products may contribute to the observed urinary levels of mono-esters (metabolites of phthalate esters) in humans. However infants and young children are more vulnerable to the potential adverse effects of Phthalates given their increased dosage per unit body surface area, metabolic capabilities, and developing endocrine and reproductive systems. Phthalates have potential toxic effects to the developing endocrine and reproductive systems. High doses have been shown to change hormone levels and cause birth defects.[70,71,72,73,74]
- According to **Reddy** et al, (2006) phthalate esters (PE) may have an aetiological association with endometriosis. (Endometriosis is a gynaecological disorder characterised by the presence of ectopic endometrial glands and stroma. It affects approximately 15% of women of childbearing age and is consistent with the estrogen-dependent nature of the disease. It is frequently associated with chronic pelvic pain, dysmenorrhoea, menorrhagia and dyspareunia, which lead to infertility.)[75]

Phthalates and Environment (Air, Water and Soil)

- Phthalates are also very commonly found in the environment. Butyl Benzyl Phthalate (BBP), di (2-ethylhexyl) phthalate (DEHP), and Dibutyl Phthalate (DBP) elicit the most toxicity to terrestrial organisms, fish, and aquatic invertebrates. Eco-toxicity studies with these phthalates showed adverse effects to aquatic organisms with a broad range of endpoints and at concentrations that coincide with measured environmental concentrations. Studies have demonstrated that phthalates with shorter ester chains like DMP, DEP, DBP, DPP, and BBP can be readily biodegraded and mineralized. On the other hand, phthalates with longer ester chains, such as Dicyclohexyl phthalate, Dihexyl phthalate (DHP), Dioctyl phthalate (DOP), and Di-2-ethylhexyl phthalate (DEHP) are less susceptible to biodegradation.[76,77,78,79]

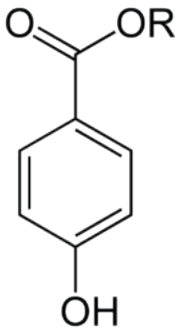
TABLE 3 - COMPILED RESEARCH STUDIES ON PHTHALATES WITH IMPORTANT FINDINGS

Year	Author	Location	Title	Important Findings
2016	**Srinivasan K., Kumaravel S. and Singaravadivel K**	Thanja-vur	*Phthalate Leach-ates in Selected Plastic Packed Food Products - A GC-MS Study*	The leaching of the phthalate in sambar (when packed/served hot in plastic cups)
206	**Krishna Kumar Selvaraj, Habibunisha Mubarakali, Maniraj Rathinam, Lakshmi Harikumar, Srimurali Sampath, Govindaraj Shanmugam & Babu Rajendran Ramaswamy**	Tamil Nadu	*Cumulative expo-sure and dietary risk assessment of phthalates in bottled water and bovine milk sam-ples: A preliminary case study in Tamil Nadu, India*	phthalates migration in packed commodities from a developing country, India, which further warrants extensive phthalates exposure assessment to understand its effect on public health
2011	**Sapna Johnson, Nirmali Saikia, Ramakant Sahu**	New Delhi	*Phthalates in Toys Available in Indian Market*	Hard and soft toys collected from Indian market found phthalates. The soft toys were contained higher levels of phthalates as compared to hard toys like rattles.

Year	Author	Location	Title	Important Findings
2006	Rastogi S K, Kesavachandran C, Mahdi F, Pandey A	Lucknow	Public health impact of plastics: An overview	The adverse health effects of phthalate exposure on human population are most likely associated with the everyday use of consumer products that commonly contain a variety of phthalates
2006	BS Reddy, R Rozati, BVR Reddy, NVVSS Raman.Association of phthalate esters with endometriosis in Indian women	Hyderabad	Association of phthalate esters with endometriosis in Indian women	phthalate esters (PE) may have an aetiological association with endometriosis.

5. Parabens

Parabens are broad-spectrum antimicrobial agents used in a range of consumer products, including personal care products, cosmetics, pharmaceutical products and food. Recently, the widespread use of parabens has raised concerns about the potential health risks associated with their endocrine-disrupting effect.[80] Chemically they are a series of parahydroxybenzoates or esters of parahydroxybenzoic acid (also known as 4-hydroxybenzoic acid). Parabens are effective preservatives in many types of formulas. These compounds and their salts are used primarily for their bacterial and fungicidal properties.[81] The general chemical structure of a paraben is shown in figure 2, where 'R' symbolizes an alkyl group such as methyl, ethyl, propyl or butyl.[82]



Usages

Consumer Products

Parabens are used in a wide variety of cosmetics as well as in foods and drugs.

Parabens and Human Health

Impacts in general

It is hypothesized that the estrogenic properties of parabens may play a role in breast cancer development. However, studies investigating the health effects of parabens are conflicting.

Impacts on women

Parabens (ester of parabenzoic acid) are a family of related chemicals that are commonly used as preservatives in cosmetic products. Preservatives may be used in cosmetics to prevent the growth of harmful bacteria and mold, in order to protect both the products and consumers. The parabens used most commonly in cosmetics are methylparaben, propylparaben, butylparaben, and ethylparaben. Product ingredient labels typically list more than one paraben in a product, and parabens are often used in combination with other types of preservatives to better protect against a broad range of microorganisms.[83]

Butylparaben is widely used by manufacturing companies for its low cost and efficiency as a microbial agent. Butylparaben is a very popular preservative because of its ability to inhibit DNA and RNA synthesis like ATPase and phosphotransferase in some bacterial species and disrupt their membrane transport proteins. It is used in various cosmetics as a preservative like eye care make up products, sunscreen, facial products and skin anti aging products. Butylparaben have

been of recent concern because of its existence in low concentration in breast tumors.[84]

In the 1990s, parabens were deemed xenoestrogens– agents that mimic estrogen in the body. "Estrogen disruption" has been linked to breast cancer and reproductive issues.[85]

The general presumption that the preservative laden personal care products may be one of the causative agents for breast cancer has remained a matter of controversy during this decade. Extensive studies have not been carried out to either prove or disprove the role of preservatives in breast cancer incidences. In this study, we have developed a new method for the identification and quantification of the preservatives such as methyl paraben (MeP), ethyl paraben (EtP), propyl paraben (PrP) and butyl paraben (BuP) in breast tissue using Gas Chromatography and Mass Spectrometry (GC–MS). Tissue was extracted by using acetone:n-hexane mixture (1:1 v/v) and derivatized with N-Methyl-N-(trimethylsilyl) trifluoroacetamide (MSTFA). The extent of reaction time and the amount of MSTFA to attain greater derivatization were optimized. The developed method yielded good recovery (mean± SD) of 99.8±5.1, 96±4.4, 107±17 and 113±13% with relative standard deviations (RSDs) of 5.1, 4.6, 15.6 and 13%, and the limits of detection (LOD) of 2.02, 1.05, 1.71 and 3.75 ng g−1 for MeP, EtP, PrP and BuP, respectively. The method was successfully validated for the determination of parabens including butyl paraben (log Kow= 3.57) in cancerous breast tissues; this could be a promising one for screening of breast tissues and also the environment for paraben residues. As far as our knowledge goes this is the first GC–MS method for the determination of parabens in human tissue.[86]

"Estrogen disruption" has been linked to breast cancer and reproductive issues

Parabens and Environment (Air, Water and Soil)

Paraben discharge into the environment is common due to its ubiquitous usage in cosmetic products. A study on consumer available personal care products revealed that 44% of the tested products contain parabens.[87] When washing these products off the human body, they flow down the drain and into community wastewater. Once this occurs, the potential for parabens to accumulate within aqueous and solid mediums materializes. Some of the most common paraben derivatives found in the environment include methylparaben, ethylparaben, propylparaben, and butylparaben. Parabens flow from wastewater to wastewater treatment plants (WWTP) as influent where they are removed, chemically altered, or released into the environment through sludge or tertiary effluent.[88]

- A research study done by **R. Karthikraj**, et al., in 2017 is the first kind of study that determined the concentrations of parabens and their metabolites in Indian STPs. The measured concentrations were high in STPs in India, suggested that these chemicals are widely used in this tropical country. The total concentration of parabens (sum of parent parabens and their metabolites) was in the range of 4360– 34,900 ng/L and 2610–3820 ng/L in influents and effluents, respectively. Paraben metabolites accounted for 93–99.6% of the total concentrations. High concentrations of parabens and their metabolites measured in effluents suggest the need for effective sewage treatment.[89] The paraben is known for an antibacterial properties but a study done by **Krishna Kumar Selvaraj**, et al, in 2013 showed the bacterial resistance against the paraben, (both bacteria and paraben were isolated from sewage treatment plant effluents in India). The susceptibility was in the order of *Staphylococcus aureus* > *Bacillus sp.* >*Escherichia coli* > *Pseudomonas aeruginosa*.[90]

Parabens and Animals

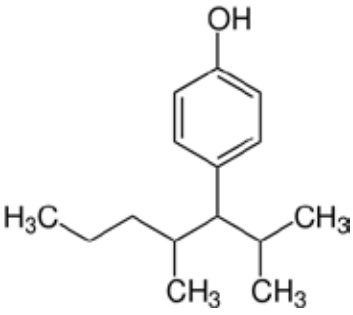
Parabens and their byproducts were found in dolphins and other marine mammals while the researchers did the study of coastal water at the United States.[91] But no such studies were found in Indian context.

TABLE 4: COMPILED RESEARCH STUDIES ON PARABENS WITH IMPORTANT FINDINGS

Year	Author	Location	Title	Important Findings
2017	**Rajendiran Karthikraj, Anuji K. Vasu, Keshava Balakrishna, Ravindra K. Sinha, Kurunthachalam Kannan**	Northeastern India and Southern India	*Occurrence and fate of parabens and their metabolites in five sewage treatment plants in India*	Determined the concentrations of parabens and their metabolites in Indian STPs.
2013	**K. K. Selvaraj, Senthilkumari Sivakumar, Srimurali Sampath, Govindaraj Shanmugam, Umamaheswari Sundaresan and Babu Rajendran Ramaswamy**	Tamil Nadu	*Paraben resistance in bacteria from sewage treatment plant effluents in India*	The study showed the bacterial resistance against the paraben.

6. Nonylphenol

Nonylphenol is an organic compound of the wider family of alkylphenols. It is a product of industrial synthesis formed during the alkylation process of phenols, particularly in the synthesis of polyethoxylate detergents. Because of their man-made origins, nonylphenols are classified as xenobiotics.[92] Nonylphenol released as a by-product of degradation of Nonylphenol ethoxylates (NPEs). NP (C15H24O) is a compound which has numerous isomers. The side chain has nine carbons and can be attached to phenol at different points on the ring, thus producing different isomers. 4-NP is the most common commercial forms of NP. NP is a clear to pale yellow viscous liquid at room temperature with moderate water solubility and moderate vapour pressure. NPEs are clear to light orange oily liquids or waxy solids, and are considered to be chemically stable and unreactive. NPEs are manufactured by reacting NP with ethylene oxide (EO) under basic conditions.



Usages

Consumer Products

- NPE is used in textile manufacture as a cleaning, dyeing and rinsing agent
- synthetic surfactants in Laundry and cleaning products ,

- Lubricating oil additives,
- Emulsifiers
- It can also be used to produce tris (4nonylphenyl) phosphite (TNPP), which is an antioxidant used to protect polymers, such as rubber, vinyl polymers and antioxidant used to protect polymers, such as rubber, vinyl polymers,

Stabilizer in plastic food packaging.

- Barium and calcium salts of nonylphenol are also used as heat stabilizers for PVC

Nonylphenol and Human Health

Nonylphenol have estrogenic effects in the body. They are known as xenoestrogens. Estrogenic substances and other endocrine disruptors are compounds that have hormone-like

effects in both wildlife and humans. Xenoestrogens usually function by binding to estrogen receptors and acting competitively against natural estrogens.[93] There is little evidence for any significant effects of exposure to nonylphenol ethoxylates on human health. However, exposure to high levels of nonylphenol ethoxylates may cause irritation of the lungs, digestive system, skin and eyes. Drinking water that has nonylphenols (excess quantity) value may cause adverse health effects.

Impacts on children

NPEs and NP may threaten the health of the developing fetus and young children.[94]

Impacts on women

A subcutaneous injection of nonylphenol in late pregnancy causes the expression of certain placental and uterine proteins, namely CaBP-9k, which suggest it can be transferred through the placenta to the fetus. It has also been shown to have a higher potency on the first trimester placenta than the endogenous estrogen 17β-estradiol. In addition, early prenatal exposure to low doses of nonylphenol causes an increase in apoptosis (programmed cell death) in placental cells.[95]

Nonylphenol and Environment (Air, Water and Soil)

Normally after a use, residuals (surfactant) get discharged into the sewage system directly or indirectly and most of them end up dispersed into the environment. Nonylphenol ethoxylate including other chemical could be present in the discharged wastewater. Nonylphenol ethoxylate gets converted into nonylphenol after biodegradation. Nonylphenol Ethoxylate degrades within hours or day to nonylphenol which is the main concern for health and environment.[96] Nonylphenol is considered to be an endocrine disruptor due to its ability to mimic estrogen and in turn disrupt the natural balance of hormones in affected organisms.[97]

- This Nonylphenol is responsible for damaging the biodiversity of aquatic environment. The effects of nonylphenol in the environment are most applicable to aquatic species. Nonylphenol can cause endocrine disruption in fish by interacting with estrogen receptors and androgen receptors. There are many articles focusing the issues of textile pollution (from different parts of the country, Tamilnadu, Gujarat, Rajasthan) but majorly they covered the heavy metals, physicochemical parameters etc. in their research, but very few articles[98] which showed the presence of nonylphenol in wastewater and its impacts on fishes. Hence, there is a need to carry out a proper study to bring this issue in public domain. In August 2016 Central Pollution Control Board (CPCB) also included all the phenolic compounds (including nonylphenol and BPA) in their PARIVESH issue.[99]
- Nonylphenol persists in aquatic environments and is moderately bioaccumulative. It is not readily biodegradable, and it can take months or longer to degrade in surface waters, soils and sediments. Nonbiological degradation is negligible. Many products that contain nonylphenol have down-the-drain applications, such as laundry and dish soap, so the contaminants are frequently introduced into the water supply. In sewage treatment plants, nonylphenol ethoxylate degrades into nonylphenol, which is found in river water and sediments as well as soil and groundwater. Nonylphenol photodegrades in sunlight, but its half life is estimated to be more than 60 years. Although the concentration of nonylphenol in the environment is decreasing, it is still found at concentrations of 4.1 microgram per liter in river waters and 1 mg/kg in sediment.
- **Krishna Kumar Selvaraj** et al in 2014 analysed the surface water samples of the three rivers viz. Kaveri, Vellar and Tamiraparani for nonylphenol concentration and observed the varied levels of nonylphenol in it. The observed concentrations were ND–2200 ng/L, in Kaveri River, 22.4–158 ng/L in Vellar River and ND–1455 ng/L Tamiraparani River. The authors concluded that such high concentrations may pose a threat to the aquatic life.[100]

Nonylphenol and Animals

Animal studies have indicated that exposure to nonylphenols can result in kidney effects over time. At higher doses, adverse developmental effects occurred including decreased weight and changes to the timing of milestones during puberty, its exposure has also been associated with breast cancer. Nonylphenol mimics estrogen and is therefore endocrine-disrupting compound.

- A research study done by **K.P. Asifa**, and **K.C. Chitra** in 2016 showed alterations in the antioxidant defence system after acute exposure to Nonylphenol. The researchers were exposed the fishes to nonylphenol at one-fifth (178 µg/ L) and one-tenth (89 µg/ L) of LC50 concentrations for 24, 72 and 96hrs to study the alterations in hepatic antioxidant defense system. Nonylphenol exposure did not alter the body weight of fishes whereas the weight of liver decreased significantly after 96 hrs at both concentrations as compared with the control groups.[101]

Subcutaneous injections of nonylphenol in late pregnancy causes the expression of certain placental

- Haematological parameters has been recognized as valuable tool for monitoring fish health. **Madhu Sharma** and **Pooja Chadha** in 2015 studied the haematological profile of fresh water fish Channa punctatus. Fish were exposed to sub lethal concentration of 4- nonylphenol decided after LC50 determination for a period of 24, 48, 72 and 96 hrs. In haematological profile, effect of 4-nonylphenol has seen on RBC count, HB, PCV, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC) which were decreasing its values and increasing in case of WBC count. The study concluded that the 4-nonylphenol caused haemotoxicity in fish.[102]
- **K. C. Chitra** and **P. P. Mathur** in 2004 studied the effect of Vitamin E on nonylphenol toxicity and their results suggested that nonylphenol induced oxidative stress in the testis of rats could be reversed by the administration of vitamin E.[103]

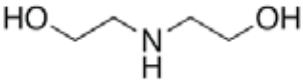
TABLE 7: COMPILED RESEARCH STUDIES ON NONYLPHENOL WITH IMPORTANT FINDINGS

Year	Author	Location	Title	Important Findings
2016	**K.P. Asifa and K.C. Chitra**	Kerala	*Alteration in hepatic antioxidant defense system induced by nonylphenol in cichlid fish, Etroplus maculatus (Bloch, 1795)*	The acute sublethal toxic effects of nonylphenol on Etroplus maculatus that was revealed by altering antioxidant defense system and also upset the membrane transport and structural integrity of hepatocytes.
2015	**Madhu Sharma and Pooja Chadha**	Amritsar	*Acute Toxicity of 4-nonylphenol on Haemotological profile of Fresh water Fish Channa punctatus*	A study showed that 4NP is hematotoxic to C. punctatus. The exposure of fish to NP resulted in significant reduction in the studied haematological parameters. These alterations may negatively suppress normal growth, reproduction, immunity and even survival of fish in natural environment as well as culture conditions.

Year	Author	Location	Title	Important Findings
2014	**Krishna Kumar Selvaraj, Govindaraj Shanmugam, Srimurali Sampath, D.G. Joakim Larsson, Babu Rajendran Ramaswamy**	Tiruchirappall	*GC–MS determination of bisphenol A and alkylphenol ethoxylates in river water from India and their ecotoxicological risk assessment*	High concentration of nonylphenol were observed in surface water of three rivers in the south part of India
2004	**K. C. Chitra and P. P. Mathur**	Pondicherry	*Vitamin E prevents nonylphenol-induced oxidative stress in testis of rats*	Nonylphenol induced oxidative stress in the testis of rats could be reversed by the administration of vitamin E

7. Di-ethanolamine

Diethanolamine, often abbreviated as DEA or DEOA, is an organic chemical compound and is soluble in water. Recently, the chemical has been classified by the International Agency for Research on Cancer as "possibly carcinogenic to humans (Group 2B)".[104] Diethanolamine is widely used in the preparation of diethanolamides and diethanolamine salts of long-chain fatty acids that are formulated into different products. Diethanolamine is used in a number of consumer products, such as shampoos, cosmetics, and pharmaceuticals.[105]



Usages

Consumer Products

- Soaps and surfactants used in liquid laundry
- Dishwashing detergents
- Cosmetics, shampoos, and Hair conditioners
- Diethanolamine is also used in Textile processing
- In industrial gas purification to remove acid gases
- As an anticorrosion agent in metalworking fluids
- In preparations of agricultural chemicals
- Aqueous diethanolamine solutions are used as solvents for numerous drugs that are administered intravenously

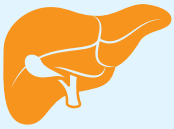
Diethanolamine and Human Health

Health impacts in general

Though the limited information available about health impacts of Di-ethanolamine, this chemical has been classified as harmful by The European Union based on its threat to human health from its continuous exposure[106] but it has not classified as carcinogenic as per EPA classification.[107] In laboratory experiments, exposure to high doses of these chemicals has been shown to cause liver cancers and precancerous changes in skin and thyroid.[108,109] There is no information available on chronic (long-term), reproductive, developmental, or carcinogenic effects of diethanolamine in humans but the acute (short-term) inhalation exposure to diethanolamine in humans may result in irritation of the nose and throat, and dermal exposure may irritate the skin. The most probable route of exposure to diethanolamine is dermal exposure as well as occupational exposure.[110]

- Di-ethanolamine also acts as hormone disruptor, with limited evidence of carcinogenic property and is known to deplete the body of choline needed for fetal brain development. DEA can also show up as a contaminant in products containing related chemicals, such as cocamide DEA.[111]

- A study done by **Panchal S.** et al in 2013 on Diethanolamine Cytotoxicity on Red Blood Corpuscles concluded that DEA is cytotoxic which caused concentration-dependent increase in hemolysis. This hemolysis may be due to alteration in membrane and oxidative damage.[112]



high doses of diethanolamine has been shown to cause liver cancers and precancerous changes in skin and thyroid.

Diethanolamine and Environment (Air, Water and Soil)

Production of diethanolamine and its wide use in industrial and consumer products may result in its release into the environment.[113,114]

Diethanolamine and Animals

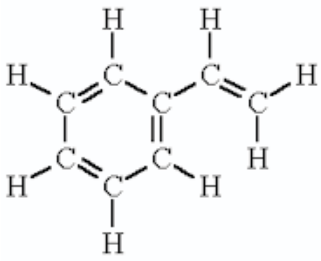
In case of animals, the studies have reported effects on the liver, kidney, blood, and central nervous system (CNS) from chronic oral exposure to diethanolamine. The National Toxicology Program (NTP) also reported an increased incidence of liver and kidney tumors in mice from dermal exposure to diethanolamine.

TABLE 8: COMPILED RESEARCH STUDIES ON DIETHANOLAMINE WITH IMPORTANT FINDINGS

Year	Author	Location	Title	Important Findings
2013	**Sneha Panchal, Heena Prajapati and Ramtej Verma**	Ahmedabad	*Diethanolamine Cytotoxicity on Red Blood Corpuscles*	**Di-ethanolamine** is cytotoxic which caused concentration-dependent increase in hemolysis

8. Styrene

Styrene is an organic compound with the chemical formula C6H5CH=CH2. It is also known as ethenyl benzene, vinyl benzene, and phenyl ethene. This derivative of benzene is a colorless oily liquid that evaporates easily and has a sweet smell, although high concentrations have a less pleasant odor. Styrene is the precursor to polystyrene and several copolymers. Global production of styrene in 2010 was 25 million metric tons.[115] Styrene is named for storax balsam, the resin of Liquidambar trees of the Altingiaceae plant family. Styrene occurs naturally in small quantities in some plants and foods (cinnamon, coffee beans, and peanuts),[116] and is also found in coal tar.[117]



Usages

Consumer Products

Styrene is named for storax balsam, the resin of Liquidambar trees of the Altingiaceae plant family. Styrene occurs naturally in small quantities in some plants and foods (cinnamon, coffee beans, and peanuts)[118] and is also found in coal tar.[119]

- **Styrene:** A petroleum byproduct that can be found in plastics, resins, and Styrofoam. It is a toxic chemical that is used to create polystyrene. CD Cases, food service products, and luggage; you name it, this chemical might be there.[120]
- **Polystyrene**: Created from Styrene, polystyrene is a lightweight, insulating material that can be in both liquid and solid form.
- **Styrofoam**: This is actually "extruded polystyrene foam," (EPS) but we just call it Styrofoam. It is made from polystyrene and is used for many things like surfboards, life rafts, bean bags, and of course as disposable plates and cups.

Styrene is essential in the creation of many products that we use every day. A few of the most familiar uses of styrene include:[121]

- The major uses are in plastics, latex paints and coatings, synthetic rubbers, polyesters and styrene-alkyd coatings[122]
- Styrofoam cups are one of many products made from styrene monomer
- Solid and film polystyrene, used in rigid foodservice containers, CD cases, appliance housings, envelope windows and many other products.
- Polystyrene foam, used in food service products and building insulation.
- Composite products, used in tub and shower enclosures, automobile body panels, wind turbine parts, boats and many other applications.

Other styrene-based materials include:[123]

- ABS plastic, used in refrigerator liners, medical devices, small household appliances and luggage.
- SAN plastic, used for food containers and optical fibers.
- SB Rubber (SBR), which reduces dependence on natural rubbers and provides improved performance in applications such as vehicle tires, leading to improved fuel efficiency.
- SB latex (SBL) used in many paper coatings and in more than 90% of the broadloom carpeting made in the United States to attach carpet fibers to a backing material.

Styrene and Human Health

The U.S. Environmental Protection Agency (EPA) and the International Agency for Research on Cancer has recognized styrene as a possible human carcinogen.[124] It has mentioned that those who work in styrene product manufacturing and are regularly exposed to high levels of styrene, then they might face irritation of the skin, eyes, upper tract and gastrointestinal effects. Its chronic exposure will lead to further complications and effects on the nervous system.[125] The symptoms of the exposure to styrene are depression, headache, fatigue, weakness and minor effects on kidney functions. Styrofoam, a material with styrene in consumer products like containers normally use for take-out food, but chemicals can leach into it and contaminate that food which affects the human health and reproductive systems. This effect is further accentuated if food is reheated while still in the container. **Never heat Styrofoam**: always remove food to a cooking vessel for reheating.

Human studies are inconclusive on the reproductive and developmental effects of styrene; several studies did not report an increase in developmental effects in women who worked in the plastics industry, while an increased frequency of spontaneous abortions and decreased frequency of births were reported in another study. Several epidemiologic studies suggest there may be an association between styrene exposure and an increased risk of leukemia and lymphoma. However, the evidence is inconclusive due to confounding factors. EPA has not given a formal carcinogen classification to styrene.[126]

Styrene and Environment (Air, Water and Soil)

Styrene takes approximately 500 years to decompose and it takes up 25-30% of our world's landfills.

Styrene is the basic building block of polystyrene and Styrofoam. Polystyrene is the biggest environmental health concern associated with polystyrene. Fifty-seven other chemical byproducts also get released during the manufacturing process of polystyrene that pollutes the air, land, water and communities that live near the facilities.[127] The public health impact of polystyrene isn't enough but its environmental effects are well documented in other countries.

Exposure to high levels of Styrene may have moderately toxic effects to wildlife, particularly aquatic organisms. At levels normally found in the environment, it is unlikely to cause significant harm. From surface waters or soils, it evaporates fairly easily into the atmosphere, where it is broken down within a few days. That which remains in soils or waters is broken down within days by bacteria. Some seepage to groundwater may occur where Styrene may persist for weeks or months. However, this is minimal as it is quickly broken down in or evaporated from soils and surface waters. Styrene does not accumulate in the environment. As a VOC, Styrene may be involved in the formation of ground level ozone, which can damage crops and materials. It is not considered likely that Styrene pollution has any effects on the global environment.[128]

Observation

From the above information (research and data) it has been observed that, the mentioned EDCs are widely used in the consumer products and researchers claim their human and environmental health impacts through their wide research. Some of the Indian researchers tried to show the direct relationships between these EDCs and animal, environmental impact in their experiments but were not able to produce much information on human health. But the research data from various international sources proved that these EDCs have acute health impacts on human health too. Further research in Indian context can support this. It is also observed that in some cases there are no standards or regulation in place; hence there has no control or restriction of its use in consumer products so it leads to the downstream contamination.

This document tried to bring out the current scenario in Indian context regarding some of the EDCs. Researchers can plan some more studies to establish the facts and based on their findings, policymakers can take appropriate actions for its use and management.

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Annexure I

TABLE 9: LIST OF COUNTRIES AND REGULATORY AGENCIES THAT HAVE DEVISED RULES FOR MONITORING EDCS

SN	Country	Regulatory agency	Mandate/strategy
1	USA	EPA-EDSP	Two-tiered in vitro and in vivo assays to identify and classify substances relative to their potential interaction with endocrine systems (Tier 1) and then to develop concentration-response relationship in animal models (Tier 2).
2	Japan	Environmental Agency-SPEED	(1) Promotion of field investigations into the present state of environmental pollution and of adverse effects on wildlife of endocrine disrupting chemicals. (2) Promotion of research and screening and testing method development. (3) Promotion of environmental risk assessment, risk management, and information dissemination. (4) Strengthening of international networks.
3	European Union	European Commission	(1) Short term strategy: to establish a priority list of candidate substances for further evaluation of their ED properties. (2) Medium-term strategy: the European Commission has made funding of research linked to ED a priority for their fifth, sixth, and seventh Framework Programmes. (3) Long term strategy includes development and adaptation of legislative instruments and policy action that enable hazard identification, risk assessment, and risk management of EDCs.

TABLE 10: AVERAGE OF BISPHENOL A (BPA) MIGRATED INTO WATER FROM THE SAMPLE CONTAINER

Sample	Migrated BPA (ng/ml)	Average concentration ng/ml)
A1	22	19
A2	19	
A3	17	
B1	19	17
B2	17	
B3	17	
C1	18	17
C2	17	
C3	18	

TABLE 11: BODY AND ORGANS WEIGHT OF CONTROL AND BPA TREATED

Treatment (For 90 days)	Initial Body weight (gms.)	Final Body weight (gms.)	Reproductive organs weight (mg/100 gm.) body weight.		
			Testis	Cauda epididymus	Testosterone level(ng/ml)
Group I Control (Vehicle Treated)	120± 1.66	160 ± 1.66	1498± 33.02	.398± .01	5.3±0.3
Group II 5µg/100g.b.wt/day	113.33±5.77	137.5±5.77	1280±43.26	361±.02	4.93±0.4
Group III 50µg/100g.b.wt/ day	115±5.77	162.5±49.24	1139 ±50.69	.335 ±.03	3.18±0.3
Group IV 100µg/100g.b.wt./ day	142.5±5.77	165±5.77	1050±71.62 *	251 ±.02 *	2.42±.8
(Mean + SEM) P<0.05			Group II, III & IV Compared with Group I		
*= significant					

TABLE 12: LEVELS OF PROTEIN IN DIFFERENCE TISSUES OF CHANNA PUNCTATUS AFTER TREATMENT WITH THREE CONCENTRATIONS OF TRICLOSAN FOR 96 HOURS

Tissue	Control	Concentration of Triclosan		
		0.1 ppm	0.5 ppm	1.0 ppm
Muscle	8.28± 0.33	6.03±0.51	4.53±0.47	3.27±0.68
Liver	6.51±0.21	4.45±0.32	3.49±0.56	2.32±0.36
Gill	5.57±0.28	4.21±0.36	3.26±0.22	2.23±0.31
Brain	4.01±0.13	3.28±0.18	2.41±0.44	1.64±0.35
Kidney	3.64±0.26	2.86±0.28	2.08±0.21	1.42±0.33
*Each value is mean of ± SD of six (6) individual observations *Values are expressed in µg/100 mg wet wt. of the tissue				

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Kidney	3.64±0.26	2.86±0.28	2.08±0.21	1.42± 0.33
*Each value is mean of ± SD of six (6) individual observations *Values are expressed in µg/100 mg wet wt. of the tissue				

Table 15 to 18 represents the Antimicrobial efficacy of different toothpastes

TABLE 14: INGREDIENTS OF VARIOUS TOOTHPASTES TESTED FOR ANTIMICROBIAL POTENTIAL

Toothpastes	Ingredients as listed on packages
I	Triclosan, Calcium Carbonate, Sorbitol, Sodium lauryl sulfate, Sodium silicate, Sodium monofluorophosphate, Sodium bicarbonate, Sodium saccharin, Carrageenan, Titanium dioxide, 1000 ppm fluoride and Flavour in aqueous base.
II	Triclosan, Sodium monofluorophosphate, Potassium nitrate, 917 ppm fluoride and Flavour.
III	Triclosan, Calcium Carbonate, Sorbitol, Sodium monofluorophosphate, Hydrated silica, Sodium lauryl Sulfate, Cellulose gum, Sodium silicate, Sodium saccharin, Potassium nitrate, Benzyl alcohol, Titanium dioxide, Water and Flavour.
IV	Neem, Pudina, Long, Babool, Turmeric, Vajradanti.
V	Miswak extract, Neem Extract, Sorbitol, Sodium lauryl sulphate, Silica, Polyethylene glycol 1500, Sodium Carboxy Methyl Cellulose, Sodium Saccharine, Sodium Benzoate, Brown Agglomerate, Treated water and Flavour.
VI	Miswak extract, Calcium carbonate, Sorbitol, Silica, Sodium lauryl sulphate, Sodium silicate, Sodium saccharin, Carrageenan, Formaldehyde, Cellulose gum, Water and Flavour.
VII	Plantago, Calendula, Hamamelis, Eucalyptus, Calcium carbonate, Sorbitol, Glycerine, Sodium lauryl sulphate, Hydrated silica, Sodium fluoride, Sodium saccharin, Cellulose gum, Water and Flavour.
VIII	Plantago major, Kreosotum, Calendula, Borax, Gel base
IX	Calendula officinalis, Hamamelis virginica, Plantago major, Aniseed oil, Calcium carbonate, Sodium fluoride and Sorbitol.
Negative Control (Toothpaste base)	Dicalcium phosphate, Carboxymethyl cellulose, Liquid paraffin, Distilled water.

TABLE 15: ANTIMICROBIAL ACTIVITY OF DENTIFRICE FORMULATIONS AGAINST *ESCHERICHIA COLI*

Toothpaste	1:01	1:02	1:04	1:08	1:16	p-value
I	33.67	33	31.83	22.17	0	0.002
II	29.17	28.67	25.67	21.5	0	0
III	32.83	31.67	31	30.17	0	0.015
IV	33.33	31.17	30.33	22.33	0	0.001
V	19.67	18	0	0	0	0.183
VI	16.33	0	0	0	0	0.417
VII	26	23	0	0	0	0.185
VIII	24.67	20.17	17.67	0	0	0.061
IX	13.5	0	0	0	0	0.417

TABLE 16: ANTIMICROBIAL ACTIVITY OF DENTIFRICE FORMULATIONS AGAINST *STAPHYLOCOCCUS AUREUS*

Toothpaste	1:01	1:02	1:04	1:08	1:16	p-value
I	22.67	22	19.67	0	0	0.046
II	29.3	24.17	23.67	14.5	0	0.016
III	24	23.5	22.67	22.67	0	0.021
IV	29.67	25.67	23.5	14.17	0	0.014
V	15.17	13.67	0	0	0	0.184
VI	13.33	13.33	0	0	0	0.185
VII	15.67	14.5	0	0	0	0.183
VIII	16.67	16	6.67	0	0	0.128
IX	16.67	14.33	0	0	0	0.184

TABLE 17: ANTIMICROBIAL ACTIVITY OF DENTIFRICE FORMULATIONS AGAINST *CANDIDA ALBICANS*

Toothpaste	1:01	1:02	1:04	1:08	1:16	p-value
I	28.17	27	21.83	15.67	0	0.049
II	33.83	26.67	28.83	20.17	0	0.14
III	31	30.5	29.67	10.83	0	0.002
IV	34	33.5	31.67	0	0	0.031
V	27	25	17.83	0	0	0.064
VI	19.83	19.33	19.17	0	0	0.052
VII	21.83	14.67	0	0	0	0.228
VIII	26.67	26	15.5	0	0	0.084
IX	16.33	15	0	0	0	0.183

TABLE 18: ANTIMICROBIAL ACTIVITY OF DENTIFRICE FORMULATIONS AGAINST *STREPTOCOCCUS MUTANTS*

Toothpaste	1:01	1:02	1:04	1:08	1:16	p-value
I	33.67	33.67	34	30	0	0.010
II	37.33	33.67	31.67	29.67	0	0.002
III	40.67	40	37.33	31.67	0	0
IV	36.63	34	36.67	030.33	0	0.009
V	20	19.33	16.33	0	0	0.047
VI	19.33	18	17.67	0	0	0.049
VII	18	0	0	0	0	0.417
VIII	28.33	28	26.33	18	0	0.002
IX	17.67	16.67	0	0	0	0.183

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