WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 8, 965-980. Review Article ISSN 2277– 7105

FAST FOOD CARCINOGENS: A REVIEW

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Article Received on
12 June 2015,

Revised on 05 July 2015,
Accepted on 27 July 2015

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ABSTRACT

The aim of this article is to study the relationship between fast food items like French fries, chips, pickles and cancer. This article focuses on acrylamide, nitrosamines, perfluorooctanoicacid, aspartame and fats and their role in carcinogenicity. Various studies conducted over the years is reviewed and a summarization of their findings is done in order to identify future research needs.

KEYWORDS: Food, Epigenetics, Salted fish, Aspartame, PFOA, Saturated fats, Carcinogenic, Nitrosamines, EPIC study.

1. INTRODUCTION

Cancer is one of the most rampant diseases in today's world. It can affect any part of the body at any age. The defining feature of cancer is the uncontrolled cell division which may lead to tumor formation. There are many types of cancer ranging from carcinoma, sarcoma, and lymphoma to the organ specific prostate, liver, urinary bladder, breast cancer etc. Cancer arises from one single cell and is usually a result of a mutation caused by a cancer causing agent called as a carcinogen. This agent results in genetic mutation or modification which the DNA repair system of the cell is unable to rectify. This is the first step of cancer.

1.1: The Disease Stages

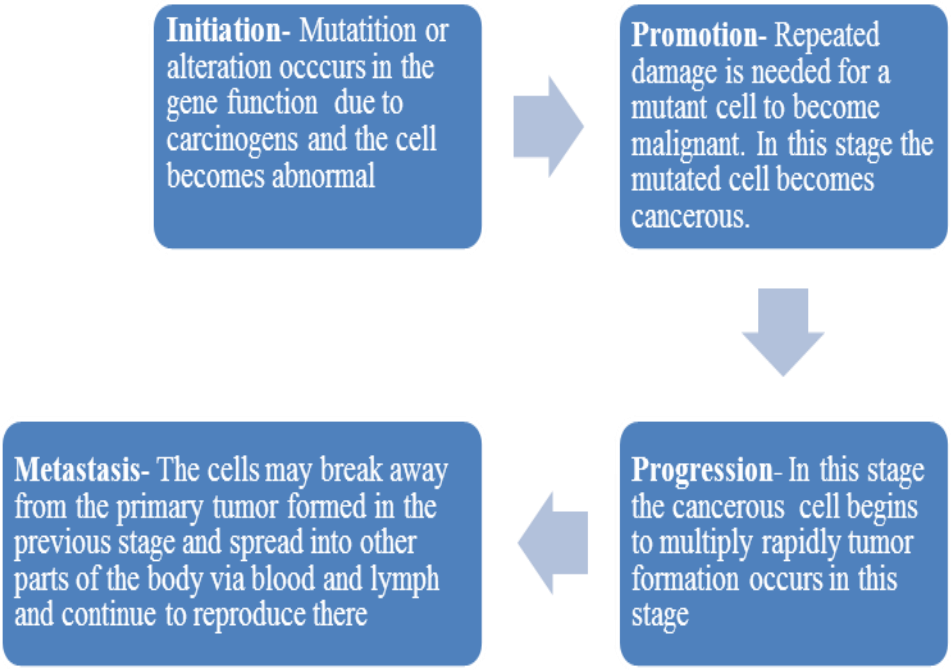

Fig. 1: Stages of Cancer

The changes from an abnormal cell to a cancerous cell is brought by agents called as promoters. The important stages of cancer is shown in Fig. 1. Certain hormones (present in the body or in food we eat) and some drugs act as promoters. Avoidance of these promoters by modifying diet and lifestyle can help in reducing the chances of cancer.[1] [2] [3] [4] [5] [6] [7] [8]

1.2: Risk Factors

Lifestyle choices like smoking, alcohol consumption, multiple sex partners, excessive consumption of red meat and processed food, drug abuse etc. further add to the risk factors of cancer. More than 30% of cancer deaths could be prevented by modifying or avoiding key risk factors, including: tobacco use, being overweight or obese, unhealthy diet with low fruit and vegetable intake, lack of physical activity, alcohol use, sexually transmitted HIV-infection, urban air pollution, indoor smoke from household use of solid fuels.[9]

The external agents causing cancer are classified into 3 categories as follows shown in Fig.2:

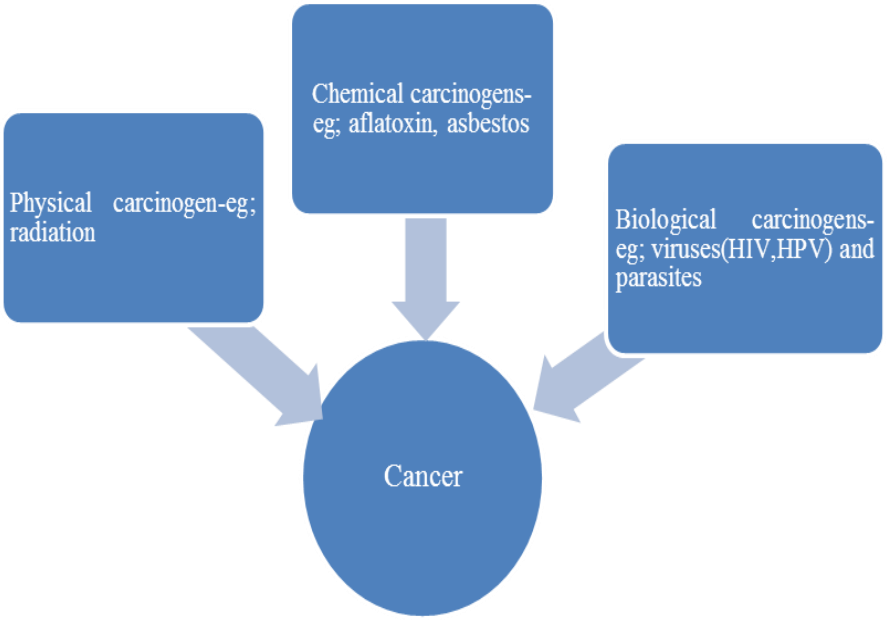

Fig. 2. External factors leading to cancer

1.3: Epigenetics

Epigenetics is the study of cellular and physiological traits that are not caused by changes in the DNA sequence but are still heritable by daughter cell. It's the study of stable and long-term alterations in the transcriptional potential of a cell. [10] It comprises several components such as DNA methylation, covalent histone modifications, particularly histone acetylation and methylation, and non-coding RNA-related mechanisms. [11] [12] [13] [14] Epigenetics has shown that many forms of cancer are caused by the chemical modifications brought forth by the environmental factors and diet. Thus the cause of these cancers is not a genetic mutation but an alteration in gene function. As a result more research is now being directed towards finding cures by altering the gene function as opposed to mutating the whole gene. Researchers now know that epigenetic modifications influence gene expression. For example, silencing of a tumor suppressor gene, which normally regulates cell growth and death, by an epigenetic modification rather than by a mutation of the gene itself. Thus it can be said that these modifications play an important role in the development of diseases, including cancer.[15]

2. FOOD AND CANCER

Certain components present in food items trigger reactions that lead to epigenetic modifications responsible for cancer. These components are present in our daily food items and are listed in Table 1.

Table 1: Cancer causing components of food[16]

Food	Component
French fries, potato chips, cornflakes	Acrylamide
Red meat	Neu5GC
Processed meat	Sodium nitrite i.e. nitrosamines
Microwave popcorn	PFOA(perfluorooctanoicacid)
Salted fish	Nitrosamines
Soft drinks (diet)	Aspartame
Butter/oil/milk	Saturated fats

2.1: Acrylamide

FDA consumption surveys show that eight food items contribute to the highest levels of acrylamide intake: potato chips, French fries, breakfast cereal, toast, soft bread, cookies, and brewed coffee. [19] French fries and potato chips are one of the most widely consumed fast food item. They are cheap and easy to prepare and are available in a variety of flavors. Potatoes mainly contain carbohydrates and fats. They also have amino acids like asparagine present in them.

2.1a: Formation of Acrylamide

Potato chips and French fries are prepared by frying at temperatures higher than 120 degree C. When carbohydrate rich food is fried/cooked/baked at such high temperatures it leads to production of acrylamide in the presence of asparagine by a reaction called as Maillard Reaction. [17][18]

2.1b: Acrylamide Induced Carcinogenicity

Acryl amide has shown carcinogenicity in lab animals like rats, mice etc. however its effect in humans is still inconclusive. A study from Harvard School of Public Health and Karolinska Institute in Sweden found that there was no link between acrylamide consumption level and cancer risk. A similar study was conducted by Dr. Mucci. The study failed to establish any link between acrylamide consumption and colon cancer in women. A study was conducted in Sweden to determine link between acrylamide and breast cancer in women. The study did not yield any assured answers. [20] [21]

2.1c: Inhibitors of Acrylamide

Studies have been conducted to see if it is possible to prevent formation of acrylamide during manufacturing processes. Some studies demonstrated that use of pectin and alginic acid may inhibit formation of acrylamide. The duration for which potatoes are soaked may also play a key role in inhibiting acrylamide formation. [46]

2.2: Nitrosamines

Nitrosamines in the form of N-nitroso-compounds (NOCs) enter our system from diet, tobacco smoking, work place and drinking water. [22] [23] They also may preexist in the food we eat or they may be formed due to various reactions or processes.

2.2a: Formation of Nitrosamines

It is formed in the acidic environment of the stomach by a reaction between nitrites and the amine groups of certain proteins (Fig). [24] Preformed exogenous nitrosamines are found in cured meat products, smoked preserved foods, foods subjected to drying by additives such as malt in the production of beer and whiskey, pickled and salty preserved foods. [23]

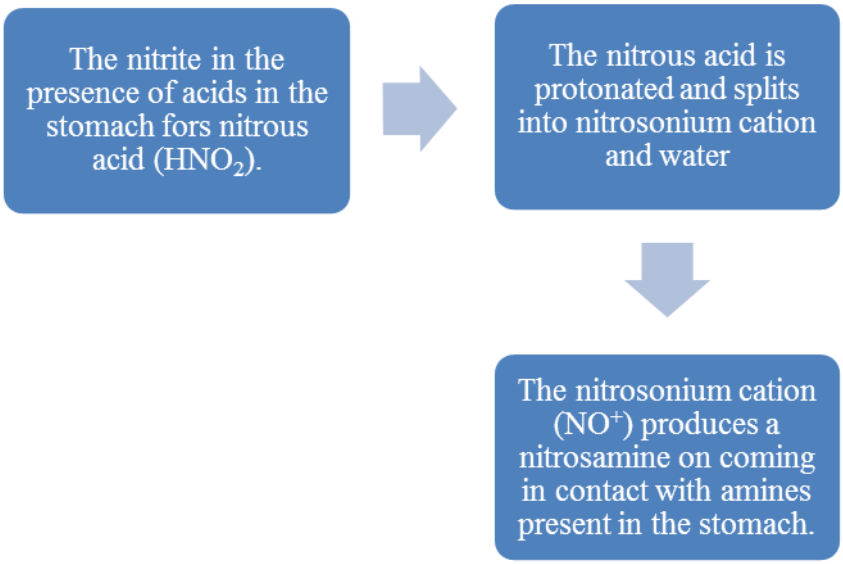

Fig. 3. Formation of nitrosamine in the stomach [25]

2.2b: Salted Fish Preparation

In Asian countries like China and Japan around 20 different types of fishes are used to prepare salted fish or fish pickle. It is a traditional Asian delicacy. [26] Salted fish may be prepared using one of the following methods:

1. **Brining**: The fish is placed in a solution of crude salt in water until its tissue absorbs the desired amount of salt.
2. **Dry-salting**: fish are mixed with dry salt till brine is formed which is allowed to drain away. Brine is solution formed as a result of the salt dissolving in the water present in the fish
3. **Pickle curing**: the fish is mixed with salt and stored in the brine formed.[27]

This process is carried out in the open. The mixture is exposed to the environment at all times for durations varying upon the type of fish, type of preparation, and till desired level of pungency and odor is achieved.

2.2c: Formation of Nitrosamines

Factors like levels of nitrites and nitrates in crude salt, high levels of amines (secondary and tertiary) in the fish coupled with the environmental conditions like presence of nitro reducing bacteria and pH may contribute to the process of formation of N-nitrosamines. [28][29][30]

Subsequent studies yielded the following results:

1. N-nitrosodimethylamine in uncooked salted fish: not detected- 388 µg/kg. Volatile nitrosamines such as N-nitrosodimethylamine, N-nitrosopyrrolidin and N-nitroso piperidine: not detected- 30 µg/kg. [31]
2. A study conducted by Zou et al., 1992 showed the levels of N- nitrosamines to be at 373 µg/kg. The samples were collected from a region having the highest nasopharyngeal carcinoma (NPC) Mortality rate. [32]

2.2d: Nitrosamines Induced Carcinogenicity

Case control studies conducted between 1980's and 1990's (period when there was high consumption of the preparation) have shown multiple cases with a positive association between salted fish and occurrence of nasopharyngeal carcinoma (NPC). Studies post this period (where consumption was less) have shown fewer cases with positive association. It was deduced that subjects who were exposed to the dish from childhood and who consumed it often were at a higher risk of NPC than those who were exposed to the dish later. The decreased consumption of the dish in the Asian countries since 1980 was also considered as a factor that may have led to decreased number of cases. [27] [33] [34] [35] [36] The exact mechanism by which NPC is caused due to nitrosamines is unknown but there is some evidence stating that activation of inactive EBV (Epson barr virus) by the nitrosamines leads to the activation of cell processes by the EBV which results in carcinogenesis. EBV present in the human body is inactive and is thus benign. [37] An increased risk for stomach cancer associated with intake of highly salty foods such as pickled fish has been observed in other populations as per a study. [38] In a Northern Chinese population consumption of salted fish more than once weekly (the most exposed individuals) was associated with a non-significant 80% increased risk, and there was no significant trend. [39] Studies showing contribution of nitrosamines in

other types of cancers like lungs, brain, prostate etc. has shown some association but found to be insufficient for evaluation. [40]

2.2e: Inhibitors of Nitrosamines

Studies of nitrosamine inhibition have consisted of the use of substances which compete with the amine for nitrosating species. [41] Some of the agents that can be used for the same are as follows:

3. Ascorbic acid- reduces the nitrosating species. [42]
4. Phenols- reduces nitrite to nitric oxide (unreactive). [43]
5. Sulfur compounds - Bisulfite reduces nitrite to nitric oxide and then to nitrous oxide Sulfamate reduces nitrite to molecular nitrogen. [44] [45]
6. Ammonium ion- reacts with nitrite to form molecular nitrogen. [45]
7. Hydroxylamine -reduces nitrite to nitrous oxide. [45]

2.3: Aspartame

Aspartame is an artificial sweetener. Aspartame is a result of combining of aspartic acid and phenylalanine which are amino acids. Aspartame being 200 times sweeter than sugar, only very little needs to be added to the beverage or food in order to attain the desired sweetness. This, in turn, lowers the calorie content of the food or beverages. [59]

2.3a: Aspartame Induced Carcinogenicity

Aspartame has been extremely controversial since its approval for use by several European countries in the 1980s. A study was conducted in 1996 to which analysed brain tumor data from 1975 to 1992 which yielded results stating that there was increase in cases. Just prior to the spike in the number of cases aspartame was introduced into the food and beverages market. This along with earlier evidence suggesting a positive association between aspartame and brain tumors in aspartame fed rats lead the researchers to believe that maybe aspartame was the causative agent. The study however lacked scientific basis. [46] Subsequently a study conducted on rats where the rats were fed varying concentrations of aspartame showed that aspartame was a multipotential carcinogen even at a daily dose of 20mg/kg of body weight. The study urged further investigation. [47]

Following these studies, the US National Cancer Institute conducted studies on humans.

Study details and results were as follows

1. They study population consisted of 285,079 men and 188,905 women ages 50 to 71 years

2. The follow up period was 5 years.
3. The study calculated the daily aspartame intake of the subjects based on aspartame consumed over the past year in the form of soda, fruit drinks, and sweetened iced tea and as sugar replacement in tea and coffee.
4. 1,888 hematopoietic cancers and 315 malignant gliomas were confirmed at the end of the follow up period. Higher levels of aspartame intake were not associated with the risk of the outcome i.e. cancer. It was thus established that aspartame does not increase the risk of brain cancer. [48]

2.4: Saturated Fats

Saturated fat is a type of single-bond animal or vegetable fat, as that found in butter, meat, egg yolks, and coconut or palm oil, that in humans tends to increase cholesterol levels in the blood. [49] They are commonly found in butter, oil, milk etc. Butyric acid, palmitic acid, lauric acid etc. are commonly existing saturated fats.

2.4a: Mechanism

It is suspected that high consumption of saturated fats leads to increase in levels of estrogen in the body which in turn may induce growth of breast cancer cells of ER and PR type i.e. hormone induced receptor positive breast cancer (Fig.4). [50]

2.4b: Saturated Fats Induced Carcinogenicity

Saturated fats have been implicated in breast cancer. The following are the types of breast cancer classified based on the expression of receptors for estrogen and progesterone on the cancer cells and over expression of protein HER2 which promotes aggressive cell growth.[50][51][52] Cancer that is not affected by number of hormone receptors is known as triple negative subtype of breast cancer.

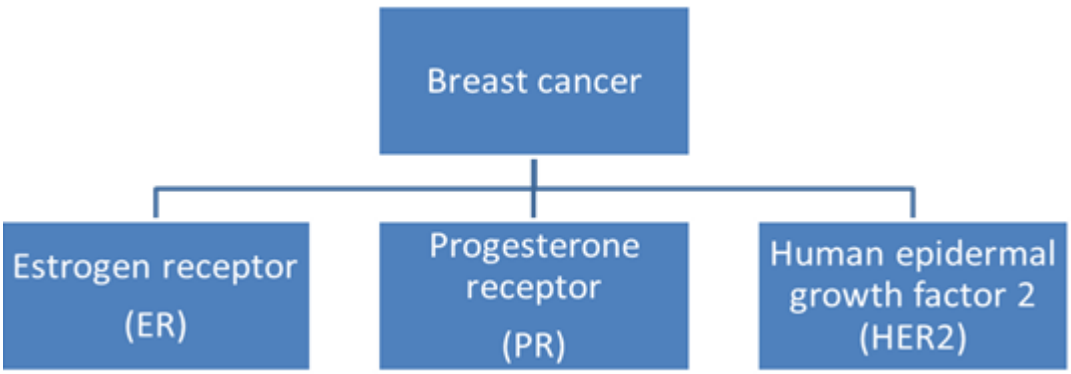

Fig. 4. Types of breast cancer

A prospective cohort study EPIC (European Investigation into Cancer and Nutrition) was conducted to investigate the effect of dietary fat on breast cancer, prospectively evaluating associations of dietary fat with breast cancer subtypes. The study involved more than 300,000 women from across Europe. After a follow up period of 11.5 years there were 10,062 cases of breast cancer were confirmed and the data was as shown in Fig. 5:

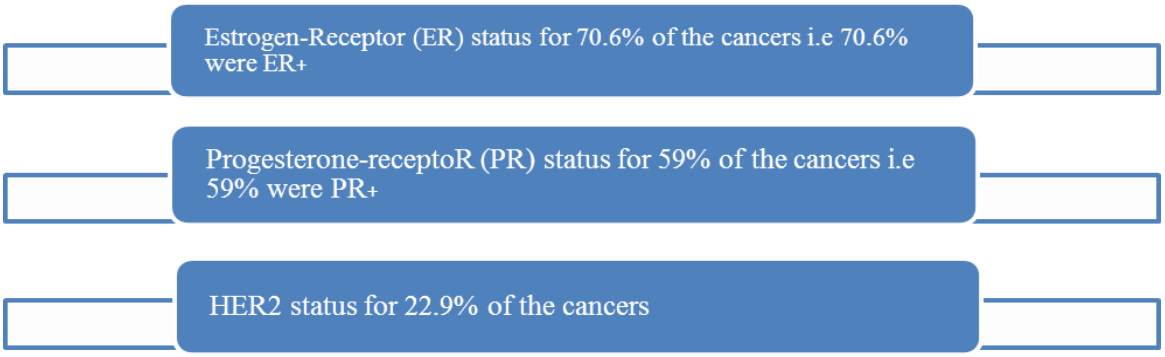

Fig. 5. Result of the EPIC study

The inference based on the follow up data were as follows

1. Women in the study who ate the most total fat had a higher risk of ER and PR subtype of breast cancer compared to women who ate the least total fat
2. Women in the study who ate the most saturated fat were at a higher risk of ER and PR subtype of breast cancer compared to women who ate the least saturated fat.
3. A higher risk of HER2 subtype of breast cancer was linked with high consumption of saturated fat It was thus concluded that there was positive association between saturated fats and breast cancer in humans. [50]

2.5: Perfluorooctanoicacid (PFOA)

Perfluorooctanoicacid acid (PFOA, or C8) is a synthetic chemical used since the late 1940s in manufacturing industrial and household products. [53]. PFOA is also formed as an unintended byproduct in the production of fluorotelomers. [54] Fluorotelomers are used in containers that store fatty or oily foodstuffs. Being lipophobic in nature they prevent the oil from soaking into the containers and compromising their integrity. [55]

2.5a: PFOA Induced Carcinogenicity

A study conducted on male rats for a period of 2 years reported that PFOA induced liver, testes, and pancreatic tumors in the test subjects. [56] Various studies were conducted on humans post this, the C8 health project being the most important one. In 2001, residents

living near Du Pont chemical plant in Washington filed a class action lawsuit alleging health damage due to PFOA-contaminated drinking water. The case was settled out of court before they went to trial and as per the settlement it was required that DuPont provide funding for a community health study called the C8 Health Project to determine the effect of PFOA on the residents. [57][58]

The study details were as follows

1. 69,030 persons between August 2005 and August 2006 were surveyed as a part of the study.
2. The eligibility criteria stated that the subjects should have lived, worked, or attended school for ≥ 1 year in one of the contaminated water districts near the plant between years 1950 to 2004.
3. Extensive residential history along with health and demographic characteristics were collected from all subjects. Serum samples were tested from the subjects for PFOA levels
4. 2,507 cancers were reported out of a sample size of 32,254 participants.
   Positive association was found between PFOA and cancer. It was thus concluded that PFOA exposure increased the risk of certain types of cancer in humans. [58]

3. OTHER DISORDERS

Apart from Cancer the constituents mentioned in this article are also suspected or proven to play a role in the onset of various other diseases shown in Table 2.

Table 2: Disorders caused by fast food ingredients. [59][60][61][62][63]

Food constituent	Disorders they may cause
Acrylamide (French fries)	Diabetes
Aspartame (canned drinks)	Phenylketonuria , Alzheimer (yet to be proved)
Saturated Fats (butter and oils)	Cholesterol
Nitrosamines (pickles and red meat)	Diabetes and Alzheimer
PFOA (nonstick ware coating)	Polymer Fume Fever – which is a type of flu which occurs due to inhalation of PFOA fumes. It is not lethal to animals.

4. CONCLUSION

The role of acrylamide in carcinogenicity in human subjects is inconclusive but it has shown strong positive association in studies conducted on animals. Acrylamide is formed during manufacture of the most widely consumed fast food like French fries and potato chips. There are methods to inhibit its formation but those are not being applied on an industrial scale yet.

The involvement of N-nitrosamines in onset of NPC is established. However the exact mechanism by which it causes carcinogenicity in humans is less understood. The exact mechanism by which it causes other forms of cancer is also unknown. Aspartames role in onset of cancer in humans is yet to be confirmed however the subject has shown to play a role in onset of brain cancer is mice. The mechanism by which it causes cancer is unknown. The involvement of saturated fats in the onset of breast cancer in humans has been established with possible mechanism.

5. FUTURE RESEARCH NEEDS

1. Further research to ascertain the role of acrylamide in carcinogenicity in humans.
2. Development of methods at a manufacturing level to prevent formation of acrylamide using asparginase, hydrocolloids, pectin etc.
3. Development of methods of preparing the French fries and potato chips at lower temperature since acrylamide is formed only at high temperatures
4. Study the mechanism by which EBV is activated by N-nitrosamines in an attempt to find a way to prevent its reactivation by N-nitrosamines.
5. Further research to ascertain role of nitrosamines in other types of cancer.
6. Test whether inhibiting formation of N-nitrosamines endogenously and exogenously can help reduces cancer cases. If results are suitable then ways can be devised to introduce the inhibitors as a part of the diet or as vaccinations.
7. Development of alternate low calorie artificial sweeteners instead of aspartame that have a lower adverse impact on the health of the consumers
8. Epigenetic studies to determine the exact role of saturated fatty acids in inset of HER2 subtype of breast cancer.
9. Studies to find out the mechanism by which PFOA causes cancer in humans
10. Development of alternates to PFOA
11. Development of methods to prevent formation of PFOA as a byproduct of fluorotelomers.

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