DISCUSSION
In the present study an attempt has been made to identify the factors responsible for breast cancer incidence in the study area of Guntur district, Andhra Pradesh. Guntur district is an agricultural region, especially with the commercial crops such as cotton, chillies, tobacco, groundnut and paddy (Pandurangadu (1988); Veeraiah and Durga Prasad (1996); Gurava Reddy (2011) where pesticides like organochlorines and organophosphates usage is more. These pesticides basing on their persistent nature and lipophilicity tend to bioaccumulate in the living organism of the trophic levels (Zhang et al, (2002); Nakata et al, (2002); Wong et al, (2002); Yang et al, (2004); Yim et al, (2005); Wurl et al, (2005); Sadler et al, (2005); Liu et al, (2007); Shegunova et al, (2007); Guo et al, (2008); Luo et al, (2009); Woudneh et al, (2009); Shahla and D'Souza (2010); Katagi (2010); Ni et al, (2011); Soto Cantu et al, (2011); Petrus et al, (2012); Mitra khani et al, (2012); Alain Demers et al, (2012); Bussolaro et al, (2012). Much work has been carried out on the effects of pesticides on human health and aquatic biota (Boatman et al, (2004); Lee et al, (2006); Boone et al, (2007); Bright et al, (2008); de Jong et al, (2008); Miranda et al, (2008); Russell et al, (2009); Amalin et al, (2009); Brittain et al, (2010); Moses et al, (2010); Chopra et al, (2011); Zhou et al, (2012). Although much work has been carried out on the adverse effects of pesticides on biota and humans, the work on carcinogenicity of pesticides and on breast cancer in the study region is not taken up earlier.

The incidence of cancer is on the rise with multiple risk factors that involve the interplay between genetic and environmental components (Roos et al, (2003); Cockburn et al, (2011). Pesticides are a major environmental risk factor (Schwartz et al, (2008); Gracia et al, (2011). In the present study the main focus was made to understand the relationship of a number of risk factors, both known and predicted with special emphasis on pesticides, with breast cancer risk.
5.1 Breast cancer risk associated with known risk factors:

The results obtained through the questionnaire and clinical pathology data confirmed that some of the established risk factors are related to breast disease in this study and some are not, depending on the classification of the patient's disease state. In this chapter, the risk factors were analysed against the breast disease continuum.

The subjects selected for the present study were women aged between 28 and 65 years. They were predominantly postmenopausal women and had children. The selected patients of the study belong mostly to rural and urban areas of Guntur district, and were mostly born in villages, where the pesticide usage is more. These results may be attributed to: genetic predisposition, environmental and change in lifestyle, and hormonal risk factors. The probability of breast cancer rises with age, but breast cancer tends to be more aggressive in younger women. This finding is consistent with previous reports and shown a higher breast cancer risk with the increasing age (Maruti et al, (2008); Alaa darweesh (2009); Van Ravesteyn et al, (2012).

There were some characteristics that may lead to breast cancer, such as: age at menarche, age at menopause, nulliparity, birth spacing, breastfeeding, oophorectomy, hysterectomy, previous breast disease (other than cancer), previous liver disease and use of hormone replace therapy. In the present study, menopausal status, number of full term births and breast feeding were analysed and showed to be a significant association with breast cancer risk. The results are consistent with the findings of Ejaz et al, (2004); Charbonneau-Roberts (2005); Hue et al, (2007); Cleary et al, (2009); Nelson et al, (2012); Boada et al, (2012) who reported that several factors were associated with lower-than-average risk, or higher; low breast density; age 15 years or older at menarche; birth of 3 or more children; breastfeeding; perimenopausal
or postmenopausal status; and use of menopausal, estrogen hormone therapy is the only treatment.

In the present study, the family historical background of the selected patients showed no statistical significance. Most of the study population has no previous history of breast cancer. There were several reports stating that some-degree of family history relates to breast cancer risk was significantly associated with high breast cancer risk (Yang et al., 2011). As such, that the results of the study were not consistent with above study reports.

5.2 Breast cancer risk associated with suspected risk factors:

In the present study, it was observed that body mass index has significant influence on breast cancer risk. For the present study the measures of weight and height were taken from the diagnostic data of the patient which was noted at the time of onset of breast cancer which may not be the correct weight. These observations were in consonance with the findings of Charbonneau-Roberts et al., (2005); Narayan et al., (2007); Brody et al., (2007); Cleary et al., (2009); Yang et al., (2011). Ali Montazeri et al., (2008) who reported that weight gain and obesity were not only the risk factors for breast cancer incidence, but also contribute to the diagnosis process.

The study regarding the oral contraceptives used, by the women in the past and present showed a statistical significance of breast cancer risk than women who have never used them. These results were consistent with the findings from previous studies that have reported the risk was highest for women, who started using oral contraceptives as teenagers. However, ten or more years after women stopped using oral contraceptives, their risk of developing breast cancer had restored to the normal level as if they had never used birth control pills (Nelson et al., 2008).
The association of tobacco smoking and chewing with breast cancer risk was studied and observed that tobacco smoking and chewing are more likely to be responsible for increased levels of breast cancer risk. The finding went hand in hand with the previous studies that have reported a significantly increased risk among current smokers compared with never smokers (RR = 1.7), moderate or strong associations between smoking and breast cancer risk (OR > 2.0) were observed in four of the eight case-control studies (Nagata Chisato et al, (2006); Boffetta and Hashibe (2006); Terry et al, (2006); Johnson et al, (2009).

The analysis of data regarding alcohol consumption and passive smoking did not show any clear link between breast cancer risk and exposure to these substances. This may be due to low consumption of alcohol in this region, whereas passive smokers were distributed in all the categories. The results were different from the finding of others who reported an increase in the incidence of breast cancer with alcohol consumption and passive smoking (Room et al, (2005); Allen et al, (2009); Boada et al, (2012).

Use of prescribed and unprescribed medication has no statistically significant risk because the pre-cancerous group uses more prescribed medicine when compared to cancerous group owing to the treatment regimes that they were undertaking for their breast conditions. Similar investigations were done by Cheryl (2007) and even they reported weak association.

Similar to the findings of Hunter (1996); Boada et al, (2012), the present study showed no contribution of dietary fat intake on the incidence of breast cancer. But the findings by Chlebowskii (2006); Prentice (2006); Gonzalez et al, (2010); Jevtic et al, (2010) showed that low-fat diets may significantly decrease the risk of breast cancer.
as well as the recurrence of breast cancer. Researchers are still not sure how to explain this apparent disagreement. Researchers are still not sure how to explain this apparent 

An increased risk of breast cancer was found in women dwelling within the area of concentrated industrial activity, the place of their work and time of exposure to chemicals, quantum of pesticide use in and around their homes, responsible for releases of chemicals that have a potential cause of breast cancer. These findings were consistent with the reports from the previous studies of cancer and environmental pollution, suggesting that people dwelling in close proximity to the above activities experience greater risk of having breast cancer Gammon et al, (2002); Kliukiene et al, (2003); Farooq Umar et al, (2010). Occupational studies on this issue were quite mixed, with some suggesting a positive association between breast cancer and work-related pesticide exposures (Band et al, (2000) and others reporting no association (Zhong and Rafnsson (1996); Sperati et al, (1999); Weiderpass et al, (1999); Dolapsakis et al, (2001); Fleming et al, (1999); (2003); Wang et al, (2002); MacLennan et al, (2003) or even a protective effect (Kristensen et al, (1996); Settimi et al, (1999).

The “lifetime applications” variable represents exposure possibility rather than an actual exposure dose. The detailed information required to calculate a received dose of pesticides was not, nor could it be, ascertained by a questionnaire alone. The categorized lifetime application variable used as the measure of pesticide exposure in these analyses allowed women to be ranked according to their reported use. The variable also enabled both reported frequency and number of years of use were combined into a single exposure variable. Finding no dose-dependent relation between exposure and breast cancer risk, this may be due to the imprecision of the exposure measure. It is possible that ever use of pesticides for individual categories
was recalled accurately, but the details of use were not. Thus, the ranks of women according to their lifetime applications may incorrectly, thereby concealing any underlying association (Faroq et al, (2010).

5.3 Pesticides exposures and breast cancer risk:

Environmental pollutants have been identified as potential inducers of breast cancer because many of these compounds have estrogen-like traits. Some of the most common and well-studied environmental pollutants are organochlorines. These include: DDE (1,1-dichloro-2,2-bis (p-chlorophenyl) ethylene), DDT (Dichloro Diphenyl Trichloroethane), DDD (Dichloro Diphenyl Dichloroethane), α, β, γ, δ- HCH (Hexa Chlorocyclo Hexane), α, β- endosulfan, endosulfan sulphate, alachlor, aldrin and dieldrin.

Organochlorines (or-GAN-oh-KLOR-eens) are a group of first generation chemicals commonly used as pesticides. Higher levels of estrogen in the blood were linked to an increased risk of breast cancer. In the present study it was observed that there was a potential for organochlorine pesticides to be the risk factor for breast cancer by measuring the levels of a series of organochlorine pesticide residues in the tissue and blood samples from the study population with breast cancer development, and identified the presence of endosulfan, DDT, HCH with the highest concentrations (Table: 4.5.a, 4.5.c). The levels of β-HCH were higher in the biopsy tissue taken from women with invasive cancer compared with the benign breast biopsies but this was not statistically significant (p=0.06). The levels of the organochlorine pesticides identified in the study were fairly consistent with the findings depicted in the previous studies suggesting a strong correlation between serum and adipose tissue concentrations of various organochlorines (Jennifer et al, (2005); Xu et al, (2010); Boada et al, (2012) and strong correlations between various adipose tissue (Ejaz et al,
(2004); Jennifer et al, (2005). However, some studies have not observed similar associations (Mozzachio et al, (2008).

Suzanne et al, (2005) reported that organophosphate insecticides (chlorpyrifos, dichlorvos, and terbufos) were associated with a higher risk of breast cancer in premenopausal women, and in women exposed to these pesticides. The present findings (Table: 4.5.b, 4.5.d) were consistent with the above report.

The present study suggests that the number of pesticides identified in tissues may not be related to the risk factors for breast cancer. It would be expected, however, that the pesticides identified in the present study and their respective concentrations in the breast adipose tissue and in blood samples were in breast cancer women when compared with benign group living or working in areas where pesticides have been used.

5.4 Role of steroid hormones in inducing breast cancer:

Environmental factors probably play a prominent role in breast cancer etiology. Breast cancer incidence has been rising steadily in many countries and it has been suggested that part of the increase may be due to the unexplained environmental factors (Ray (1997). Chemicals such as pesticides and herbicides have been suggested to be able to interact with the endocrine system (Kristensen et al, (2001). Numerous environmental chemicals have also been shown to possess estrogenic activity by virtue of their ability to bind to the ER (Lucier (1992). Straube et al, (1999) found changes in androgen concentrations and lymphocytes in relation to pesticide exposure; effects of chronic exposure were expressed by a higher level of testosterone (Straube et al, (1999); Garry et al, (1999) and an alteration of testosterone/SHBG ratio (Abell et al, (2000).
Levels of sex steroid hormones—estradiol, progesterone and testosterone in serum were hypothesized to increase breast cancer risk. The study analysis observed a significant increase in serum levels of hormones associated with increased risk of breast cancer in both benign and cancer groups. This analysis was in agreement with the reports of (Althuis et al, 2004; Potter et al, 1995; Chen et al, 2004; Tjonneland et al, 2004) who observed that breast cancers classified by estrogen receptor (ER) and progesterone receptor (PR) expression not only have different clinical, pathologic, and molecular features, but may also be etiologically distinct. But Sieri et al, 2009) reported that high levels of circulating testosterone increase the risk of developing breast cancer in postmenopausal women and opposing associations with estrogen. Miyoshi et al, 2010) reported that estradiol level was not a reliable risk predictor for postmenopausal women, perhaps because of the low levels detected; preferring estrogen levels instead.

Estrogens were known to stimulate directly the proliferation of breast cells, whereas the effect of androgens on breast tissue is more complex and still unclear. Shufelt et al, 2008) reported that the conversion of androgens into estrogens may be a possible mechanism by which androgens stimulate proliferation of the breast cells. The aromatase enzyme is responsible for the conversion of androgens into estrogens and it may control the local production of estrogens through an autocrine loop (Laura Baglietto et al, 2010). Significant association was observed between androgens and breast cancer risk and with the highest concentrations in true cancer women However, Hankinson et al, 2007; Kaaks et al, 2005 observed an association between androgen levels and breast cancer risk can be decreased after adjusting for estrogen levels. Both these findings are consistent with the argument that the contribution of androgens to breast cancer might be largely through their role as estrogen precursors.
and that at older ages, aromatase activity increases to maintain high concentrations of estrogens in the breast tissues. The present findings were in agreement with the above reports.

5.5 Breast Cancer and Single Nucleotide Polymorphism:

Polymorphic changes in VEGF, h-RAS and ESD were observed in most of the cancer group blood samples. The vascular endothelial growth factor (VEGF) is an important regulator of angiogenesis in the process of tumor growth and vascular permeability. Polymorphisms in the VEGF gene have been associated with altered VEGF expression and plasma VEGF levels. VEGF over expression has been associated with advanced stage and poor survival of several cancers. The association of functional polymorphisms in the VEGF gene with breast cancer survival was elevated in the present study. Important new insights into the molecular epidemiology and genetics of breast cancer was provided in the recent past Genetic factors and their interactions with environmental risk factors for breast cancer, may have greater public health importance.

A significant association of rare h-RAS (Hoenerhoff et al, (2009) alleles with breast cancer was observed in the present study. However, the biological mechanism underlying this relationship remains unclear. The allele products encoded by these genes function in signal the transduction pathways, mutations in this gene cause Costello syndrome, a disease characterized by increased growth at the prenatal stage, growth deficiency at the postnatal stage, predisposition to tumor formation, mental retardation, skin and musculoskeletal abnormalities, distinctive facial appearance and cardiovascular abnormalities (Masood et al, (2011). Defects in this gene are implicated in a variety of cancers, including bladder cancer, follicular thyroid cancer,
and oral squamous cell carcinoma. Multiple transcript variants, which encode different isoforms, have been identified for this gene (Ref Seq, (2008).

*ESD* gene encodes a serine hydrolase that belongs to the esterase D family. The encoded enzyme is active toward numerous substrates including O-acetylated sialic acids, and it may be involved in the recycling of sialic acids. This gene is used as a genetic marker for retinoblastoma and Wilson's disease. (Ref Seq, (2009)

### 5.6 *In vivo* studies on pesticide effects in Albino rats:

In epidemiological studies, exposure to pesticides has been associated with menstrual cycle disturbances, reduced fertility, prolonged time-to-pregnancy, spontaneous abortion, stillbirths, and developmental defects, which may or may not be due to disruption of the female hormonal function. Because pesticides comprise a large number of distinct substances with dissimilar structures and diverse toxicity, it is most likely that several of the above-mentioned mechanisms are involved in the pathophysiological pathways explaining the role of pesticide exposure in ovarian cycle disturbances, ultimately leading to fertility problems and other reproductive effects. Animal studies offer an advantage of a closely situation, though extrapolation to a highly variable human population is beset with problems, though animal studies test a single hypothesis but they complement human studies.

In the present study, the effects of endosulfan, aldrine, malathion, chlorpyrifos and their combinational effect on steroid hormones of albino rats were studied and observed a statistically increased activity of estradiol (E2) (Table: 4.16), progesterone (P4) (Table: 4.17) (Figure: 4.26) and testosterone (T) levels in all treated groups (Table: 4.18). The presently observed changes were in agreement with the observations of Ulla Hass *et al*, (2012); Vinggaard *et al*, (2005); Willingham *et al*,
who found an association between hormones and pesticides both in vivo and in vitro.

5.6.1 Single Nucleotide Polymorphism changes in Albino rats:

The present study demonstrated that the mammary tissue of rats is sensitive to the carcinogenic actions of chemicals such as Endosulfan, Aldrin, Malathion, and Chlorpyrifos, the last two normally are not inducing breast tumors. Single nucleotide polymorphic changes were seen in the albino rats treated with Endosulfan, Aldrine, malathion, chlorpyrifos combination and SNP change of h-RAS, ESD and VEGF genes was found in fourth week treated animals. High change was observed in VEGF gene. This study is consonance with Mitsumori et al., (1998); Yamamoto et al., (1998); Reddy et al., (1975); Thorup et al., (1995); Masumura et al., (2003).

Tumors observed in h-RAS 128 rats were mammary carcinomas and squamous cell papillomas in the back and the scrotum skin. Histological types of mammary carcinomas were tubular with a cribriform arrangement, solid tubular or papillary tubular (Figure: 2). (Cardiff et al., (2000) reported that, histological examinations of all major organs, including the esophagus, fore stomach, tongue, and urinary bladder, which were also found to be highly susceptible to chemical carcinogens in h-RAS 128 rats, no tumors were found, possibly due to the relatively short duration of the observation period and low doses of carcinogens.

In some studies, such mutations have been already evident in end buds (Hamaguchi et al., (2004) postulated tissue targets of carcinogens (Russo et al., (1979); (1983) before the obvious proliferative change occurred. Thus, it is possible that test compounds including non mammary carcinogens might also cause mutation of the transgenes, a possibility which we are presently exploring. In the present study, most mutations were of transversion type in codon 12, GGC to GTC predominating,
irrespective of the chemical carcinogen. Clearly, it is necessary to analyse whether transversion clustering is dependent on the carcinogen administered or the organ in which the tumor appears. The study goes hand in hand with the findings of Tennant et al, (1995); Tsuda et al, (1999).

Furthermore, this model can be used for the assay of modifying agents including chemopreventive compounds (Matsuoka et al, (2003) and also nongenotoxic promoting agents (Fukamachi et al, (2004); Tsuda et al, (2005). Given the number of compounds released into our environment, further validation studies using h-RAS, VEGF and ESD is necessary.

5.6.2 Pesticide exposure and histopathological changes in albino rats:

The study is designed to determine the consequences for reproductive development and function resulting from in vivo exposure to a mixture of environmental toxicants. The present investigation indicates that oral exposure to endosulfan, aldrin, malathion, chlorpyrifos and the mixture of these compounds caused significant alterations in histological architecture.

The liver is the primary organ involved in xenobiotics metabolism and is a major target organ for chemicals and drugs. Hepatotoxicity is therefore an important aspect in the evaluation of the effect of particular xenobiotics. Endosulfan is one of the main causes of poisoning in humans in many countries (Kishi et al, (2002); Oktay et al, (2003); Roberts et al, (2004); Wesseling et al, (2005).

The research work on the effect of Endosulfan was studied in albino rats and an observed interference of endosulfan with mammary gland development by increasing the number of alveolar buds and by increasing telomerase reverse transcriptase mRNA transcriptional activity. Evidence of the carcinogenicity of
endosulfan is regarded as being inconclusive. The observations were similar to the findings of Je et al., (2005); Reuber (1981) and they reported an increase in the total number of malignant tumours and pulmonary adenomas, and increase in total number of carcinomas, hepatic carcinomas, and sarcomas in female rats, and lymphosarcomas in male rats. Other studies confirmed that α-endosulfan is a tumour promoter causing a significant and dose-related increase in hepatocytes (liver cancer cells) (Fransson-Steen et al., (1992); ATSDR (2000), and to rapidly inhibit Gap Junctional Intercellular Communication (GJIC) in liver cells (Dubois et al., (1996); Warngard et al., (1996). The tumour promoting effect is suggested to be through the inhibition of GJIC (ATSDR (2000).

Virgo and Bellward (1975) observed a significant but slight decrease in fertility in female mice exposed to 1.3 or 1.95 mg/kg/day of dieldrin from 4 weeks prior to mating through weaning where as males were exposed to test material only during the 2-week mating period. In another report, male and female rats receiving diets containing aldrin or dieldrin at doses of aldrin as low as 0.63 mg/kg/day and dieldrin as low as 0.125 mg/kg/day from the time they were 28 days old had decreased fertility (decreased number of litters) during the first mating of the parental generation in a three-generation reproduction study (Treon et al., (1954a).

The toxic effects of commercial malathion can be explained by the presence of impurities in commercial formulations and are metabolized in the liver and processed into more polar and toxic metabolites such as malaoxon, and excreted causing tubular damage in the kidney (Prabhakaran et al., (1993); Possamai et al., (2007); Reus et al., (2008). In other reports, animals exposed to acute malathion treatment caused the most sensitive targets of oxidative damage in the kidneys, lungs and diaphragm (Possamai et al., (2007). Several investigations have revealed that malathion exposure
was associated with necrosis and edema in the seminiferous tubules and interstitial
Other studies have demonstrated that chronic exposure to malathion produced signs of
histological damage in the kidney marked by hyperplasia or hypertrophy of tubular
cells and morphological alterations in the glomerulus (Bosco et al, (1997). Similar
results were found in the present study with acute exposure to malathion. These
results suggest that acute and chronic exposure to malathion will lead to long-term
human health consequences.

Malathion induced severe hepatic and renal damages as shown in
histopathological examination. Tos-Luty et al, (2003) showed that malathion
intoxication led to severe effects on the structures of the liver and kidney including
the presence of fine subcapsular infiltrations, diffused parenchymatous degeneration
of single hepatocytes, and the presence of fine foci constructed of plasmatic cells, and
histiocytes located between hepatic plates.

However, different studies showed that malathion and other pesticides induced
liver and kidney histopathological alterations in experimental animals (Yavasoglu
investigations are required to explore exactly the mechanism action of malathion-
induced physiological disturbances and histopathological changes.

The study demonstrates that chlorpyrifos, malathion and chlorpyrifos
combination, endosulfan and aldrine combinations induced tumor formation in a
specific target organ, the mammary gland. The results showed that initiation occurs
primarily in the epithelium of TEBs while they are developing into ABs because these
structures are affected by pesticides. This was an important observation because such
structures were considered equivalent to the terminal ductal lobular unit described in
the human breast. Similar observations were made by Russo (1978); (1980); (1982); (1990); (1991); Eaton et al, (2008).

These results indicated that the proliferative changes observed in the TEBs may have induced the formation of mammary adeno-carcinomas.

Synthetic halogenated organic compounds, such as dichloro diphenyl trichloroethane (DDT) and its persistent metabolite p, p – dichloro diphenyl dichloro ethane (p, p’-DDE), hexachlorobenzene (HCB), dioxins and furans, polychlorinated biphenyls (PCBs), other organochlorine pesticides, and metals such as lead and cadmium were reported as contaminants in tissues collected from the human population globally (Davies and Mes (1987); Frank et al, (1988); Mes et al, (1990); Newsome et al, (1995); Szymczynski et al, (1981a, 1981b); Warren et al, (2004). Detectable levels of suspected endocrine toxic chemicals such as p,p-DDE, α-hexachlorocyclohexane, and selected PCB congeners in second trimester human amniotic fluid have been reported (Foster et al, (2000); indicating fetal exposure to these compounds. However, the effect of these toxicants, when present together in a mixture on development or reproductive function was poorly understood. The data suggest that environmental toxicants can interact to augment the growth of mammary gland cells, function, and, ultimately, pathophysiology.

Animal experiments suggest that developmental-stage exposure to environmental toxicants is an important determinant of toxicant-induced changes in reproductive-tract and mammary gland development and the pathogenesis of mammary tumors. Specifically, prenatal and perinatal exposures to environmental toxicants were associated with an increase in mammary tumor formation (Brown et al, (1998a); Desaulniers et al, (2001); Fenton et al, (2002); Markey et al, (2001) while toxicant exposure after differentiation of the mammary gland has been linked with
either no effect or decreased risk of mammary gland tumor development (Holcomb and Safe (1994); Nesaretnam et al, (1998); Ramamoorthy et al, (1999). Mammary gland morphogenesis begins in utero and proceeds through several discrete stages as the animal ages (Russo and Russo (1978).

Earlier reports have demonstrated that mammary carcinoma formation in rats can be induced by a chemical carcinogen, mainly DMBA, in older women, had the highest growth fraction and DNA-LI in the intra lobular terminal ducts (Russo (1990); (1991). The length of the cell cycle in these structures increased from 200.3 to 847.0 hr in the older women (Cabello et al, (2001). The high rate of cell proliferation was associated with the shortened length of the cell cycle. Other reports (Russo (1978); (1980); (1982); (1990); (1991) have shown that DNA-LI among young virgin rats was much higher than among old virgin rats.

Therefore the present study proposes that in vivo exposure and early postnatal exposure to environmental toxicants will act on the undifferentiated cells of the mammary gland to alter mammary development and increase the risk of tumor formation. Indeed, in utero exposure to environmental toxicants such as TCDD and bisphenol A has been associated with delayed differentiation of the mammary gland, which has been associated with increased sensitivity to carcinogens. Mammary gland tumor numbers were augmented by prenatal treatment with TCDD (Brown et al, (1998a). These data suggest that the critical window for carcinogen-induced mammary tumors is prior to complete differentiation of the mammary gland. Hence, the exposure to environmental toxicants with a long half-life will result in exposure of the developing mammary gland prior to the differentiation of the TEB into alveolar buds and subsequently into lobules.