Experimental
ONCOLOGY

# ENDOCRINE DISRUPTING PESTICIDES: A LEADING CAUSE OF CANCER AMONG RURAL PEOPLE IN PAKISTAN

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Evidence on the relationship between cancer and occupational exposure to pesticides and endocrine disrupting chemicals is reviewed. In animal studies it has been proved that majority of endocrine disrupting pesticides are carcinogenic. In humans, pesticides have been classified as carcinogens by the International Agency for Research on Cancer. Farmers may therefore be at higher risk for acute and chronic health effects associated with pesticides. Human data, however, are limited by the small number of studies that evaluate individual endocrine disrupting pesticide. Cancer of the breast, ovary, prostate, testis, and thyroid are hormone-dependent, which fostered research on the potential risk associated with occupational and environmental exposure to the so-called endocrine-disrupting pesticides. Professional as well as public exposure to pesticides raises cancer risk. Interaction with adjuvant and with other toxicants increases the actual risk. On the other hand, organochlorine pesticides and triazine herbicides require further investigation for a possible etiologic role in some hormone-dependent cancers.
*Key Words*: cancer, pesticides, endocrine disruptors, farmer.

Agriculture in developing countries has become strongly dependent on the use of chemical substances in order to control insects and other plagues, aiming to enhance productivity [1]. However, environmental and human health problems caused by the extensive use of these chemicals, mainly of pesticides, have been reported worldwide [2]. Farmers have numerous op-portunities for exposure to pesticides, including those during planting and cultivation of crops, pesticide ap-plication to crops, mixing and preparing pesticides for application, and loading and cleaning application equip-ments [3]. Farmers may be at greater risk of pesticide exposure if they incorrectly handle, store, or dispose off pesticides or if they don't wear personal protective gear. Farmers may therefore be at higher risk for acute and chronic health effects associated with pesticides [4]. According to the World Health Organization [5], de-veloped countries consume 80% of all pesticides pro-duced worldwide. Nevertheless, due to the lack of spe-cific legislation and inefficient pesticide market regula-tion, agricultural workers from developing countries are likely to be exposed to higher levels or even to more dangerous classes of these compounds [6].

Developing organisms have increased susceptibi-lity to cancer if they are exposed to environmental toxi-cants during rapid growth and differentiation [7]. Envi-ronmental contamination by pesticides has been do-cumented in biotic and abiotic components. These persistent organic pollutants are lipid soluble, non–bio-degradable, and endocrine disrupters [8]. Exposure to chemical substances displaying a hormonal–like mo-lecular structure, generally named endocrine disrup-tors, has been gathering scientific interest as a conse-quence of the observed association with several bio-logical hazards in humans and animals [9]. Endocrine disruption, procarcinogen activation by detoxification enzymes and intercellular communication impairment are involved in the carcinogenic processes [10].

Numerous epidemiological reports allude to a posi-tive relation between pesticides and cancer [11]. Present study was basically designed to join evidence on the possible correlation between pesticides expo-sure and growing incidences of cancer, in Pakistan.

***Endocrine disrupting chemicals.*** For a number of years, concern has been growing over changes in the health and fecundity both of humans and wildlife which may be associated with the disruption of hor-monal systems by environmental chemicals [12]. An endocrine disrupter is an exogenous substance that causes adverse health effects in an intact organism, or its progeny, subsequent to changes in endocrine func-tion [13].

Endocrine disrupting chemicals (EDCs) include many naturally occurring or synthetic chemicals that are proposed to share a common mode of action by interfering with the normal molecular circuitry and func-tion of the endocrine system [14]. EDCs that act on the estrogen component of the endocrine system merit serious concern because estrogen has major effects on mammalian reproduction and neurological functions. Estrogen is also critically important for guiding the nor-mal functional and structural development of many tar-get organ systems in mammals, with effects both on

growth and differentiation. The existence of critical periods during organogenesis and the sensitivity of developmental processes to relatively small and fleeting changes in endogenous steroid levels suggest that endocrine disruption during development may have long lasting deleterious effects.

**Endocrine disrupting pesticides.**

*1,1,1–Trichloro–2,2–bis(p–chlorophenyl)ethane (DDT)*
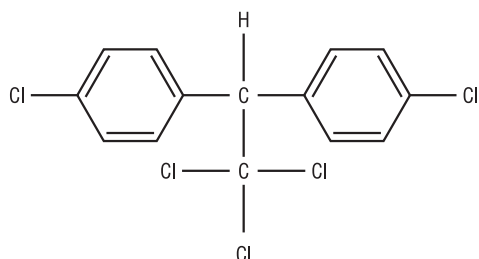
Since 1940s, dichlorodiphenyltrichloroethane (DDT) has been used worldwide as an active insecticide in agriculture, both for pest control and for vector control in human hygiene against diseases such as malaria and typhus [15]. It was not until later that DDT was found to be highly persistent in the environment [16]. As with other organochlorine pesticides, DDT compounds have been found to be toxic to human [17]. Its use was banned in developed nations after 1970; there is still an illegal use of this pesticide in Pakistan [18].

The evidence from *in vivo* animal experiments for the organochlorine pesticide DDT is unequivocal, pointing to complete carcinogenicity in the rodent liver, which is also the target for its toxicity [19]. However, there is evidence for a dose threshold and exceedingly low doses may even act in a hermetic fashion, inhibiting development of the lesions [20]. The relationship of DDT exposure and breast cancer risk has received increasing attention since the beginning of the 1990s [21]. Exposure to organochlorines may be associated with higher rates of certain cancers, particularly stomach and lung cancer [22]. DDT persist in human tissues for years, with correlated breast cancer incidence. One major point usually underestimated in risk evaluation is the individual variability in detoxification capabilities. Furthermore cellular sites of cancerisation are not necessarily identical to sites primarily exposed to toxicants [23].

*Polychlorinated biphenyls (PCBs)*
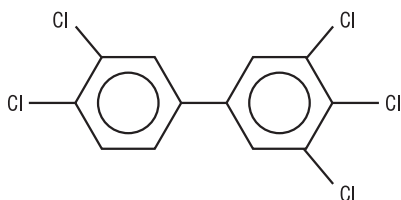
Polychlorinated biphenyls (PCBs) are a family of persistent organic contaminants suspected to cause adverse effects in wildlife and humans [24]. PCBs are complete carcinogens and promoters in the rodent liver [25]. They may act as promoters in the mouse lung [26] and may be associated with accumulation of iron in Kupffer cells and elevated proliferation of hepatocytes in the rat liver [27]. There is evidence that neo-

natal exposure to high doses of organochlorines could favor the development of MNU–induced mammary lesions, but it is also reported to delay the development of palpable tumors in the rat [28]. Some PCB congeners have shown estrogenic effects, and this has raised concern that they may increase the risk of breast cancer [29]. PCBs are known for their neurotoxic properties, especially on the developing brain [30]. Recent examination of plasma data indicated that exposure to dioxin–like PCBs increases the breast cancer risk. However, many PCBs may be more strongly associated with tumors with poor prognosis [31].

*Tetrachloro–p–dioxin (TCDD)*
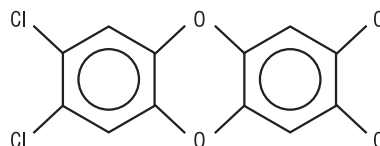
Tetrachlorodibenzo–p–dioxin (TCDD) is the most potent congener among the halogenated aromatic hydrocarbons and is a widespread environmental pollutant. It has received much attention as a developmental and reproductive toxicant with endocrine disruption capability [32]. Several studies have established that TCDD blocks ovulation [33]. Most recently, dioxins have been found in human ovarian follicular fluid. Dioxin exposure may lead to the development of endometriosis [34].

In mice and rats, TCDD is a complete hepatocarcinogen, which also causes follicular cell adenomas of the thyroid gland, squamous cell carcinomas of the nasal cavity and fibrosarcomas in different sites [35]. Impaired mammary gland development and differentiation were found in female mice and rats after gestational and lactational exposure [36]. TCDD causes cardiovascular toxicity in avian and fish embryos and disturbs craniofacial development in fish [37]. TCDD, is carcinogenic to many species, evidently including humans and acutely lethal to many laboratory animals [38]. In humans, the developmental toxicity of dioxins can appear as hypomineralized enamel defects in permanent teeth of breastfed [39]. Soft–tissue sarcoma has been proposed to be a candidate for a dioxin–induced cancer [40].

*Butylated hydroxyanisole (BHA)*
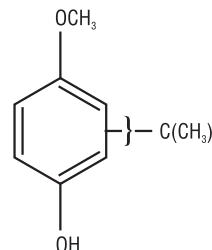
Butylated hydroxyanisole (BHA) is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals [41]. When administered in the diet, BHA induced papillomas and squamous cell carcinomas of the forestomach in rats of both sexes and male Syrian Golden hamsters. In rodents, BHA is a forestomach carcinogen, but with a dose threshold pointing to an epigenetic mode of action [42] dependent on proliferation [43]. Assessment of the

reversibility of the lesion further led to the conclusion that the tumors induced by BHA are most unlikely to be relevant to humans exposed to the agent at much lower levels [44].

*Triazines*
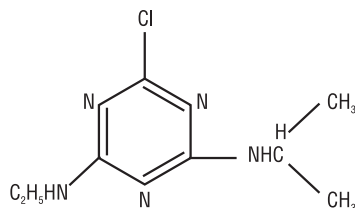


Trazine is classified as a 2B carcinogen by WHO and considered by the USEPA as a possible human carcinogen. It is linked to ovarian, breast and testicular tumors. While one study suggested a link between agricultural exposure to trazine and non–Hodgkin's lymphomas [45], the epidemiological evidence regarding triazines points to a null association for breast cancer across all exposure indices and an inverse association with ovarian cancer [46].

At high–dose in F344/LATI rats, atrazine was found to cause significant increase in the number of combined leukemias/lymphomas and also a higher incidence of mammary tumors, together with uterine carcinomas in a dose–dependent manner [47]. Regarding other findings reported, it should be noted that a significant increase in lymphomas was observed with chronic treatment of Swiss albino mice [48].

*Di(2–ethylhexyl) phthalate (DEHP)*
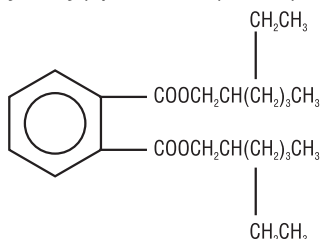


Di(2–ethylhexyl) phthalate (DEHP) is known to be widely distributed in the environment and has been detected in soil samples, animal and human tissues, and various fish and marine life. Disposal of plastic products containing DEHP is a major source of environmental release [49]. The primary routes of potential human exposure to DEHP are inhalation, ingestion, dermal contact, and through medical procedures.

DEHP, a peroxisome proliferator, has been listed by the International Agency for Research on Cancer (IARC) as a possible or reasonably anticipated human carcinogen, because it induces dose–related increase in liver tumors in both sexes of rats and mice [50]. When administered in the diet, DEHP increased the incidence of hepatocellular carcinomas in female rats, liver neoplastic nodules or hepatocellular carcinomas in male rats, and hepatocellular carcinomas in mice of both sexes [51].

Since DEHP also exerts other biological effects that occur independently of peroxisome proliferation, it is possible that some of these responses may also contribute to the carcinogenicity of this chemical [52]. It is considered that DEHP should be classified as an unlikely human carcinogen with the margin of exposure (MOE) approach to risk assessment.

*Tributyltin (TBT)*
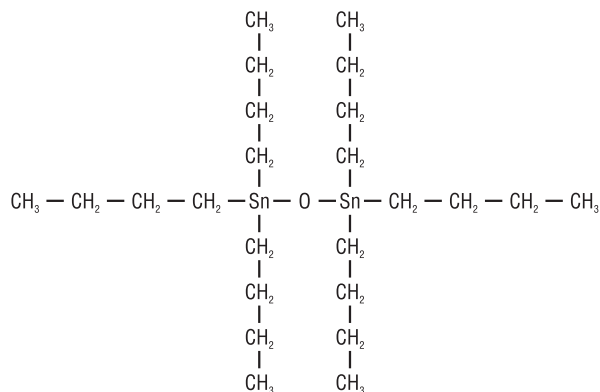


Tributyltin (TBT) is the most toxic butyltin (BT) [53]. TBT was produced in large quantities for use in wood preservation, marine antifouling paints, disinfection of circulating industrial cooling waters, and slime control in paper mills [54]. TBT is reported to cause serious health problems, particularly endocrine disruption, in lower–trophic organisms in the aquatic food chain and is suspected of immunotoxic effects in marine mammals [55].

This chemical seems to debilitate the immune function of animals, making them vulnerable to infectious diseases [56]. In terrestrial mammals TBT has been shown to affect the function of natural killer (NK) lymphocytes, which are a primary immune defense against tumors and virally infected cells [57]. NK cells are lymphocytes capable of killing tumor cells, virally infected cells, and antibody coated cells. They are responsible for limiting the spread of bloodborne metastases and for limiting the development of primary tumors [58]. Despite mounting evidence on BT contamination and related immunotoxic effects on wildlife, very little is known about BT–associated immunotoxic effects on humans. A recent study on human indicated short–term exposure to TBT causes persistent negative effects on NK cell ability to kill cancer cells and may favor the progression of cancer [59].

**Different pesticides used in Pakistan.** The agricultural productivity in Pakistan is hampered by insects, diseases, and weeds, which are reported to cause losses ranging up to 50%, estimated at a total value of over 900 million U.S dollars. Punjab is one of the biggest provinces in Pakistan, with hundreds of factories in the urban district. Agriculture is the major land–use in the surrounding suburban and rural areas.

The use of pesticides in Pakistan started in 1954 with 254 metric tons of formulation, increasing to the level of 16,226 metric tons in 1976–77 [60]. From the 1980s to 1990s, large amounts of pesticides were applied in the agricultural areas of Punjab. At present, more than 108 types of insecticides, 30 types of fungicides, 39 types of weedicides, 5 types of acaricides, and 6 different types of rodenticides are being used in Pakistan. Insecticides comprise 90% of the total pesti-
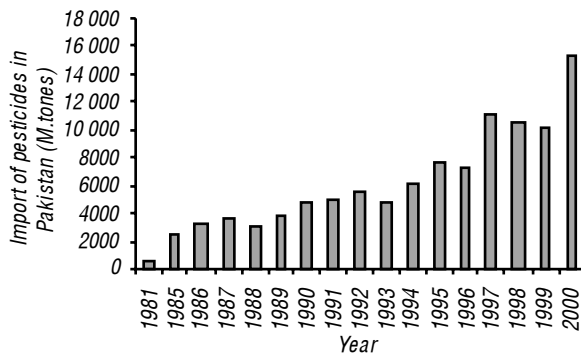
Fig. 1. Import of pesticides in Pakistan

cide consumption in this country and import of pesticides is increasing gradually every year (Fig. 1) [61].

Use of pesticide in Pakistan has increased by 1,169% in last 20 years and number of spray per crop has reached more than 10 [62], which is an alarming thing as for as human health is concerned. Some of the insecticides, herbicides, fungicides and nematicides, have been reported to display endocrine disrupting properties [63]. Several chemical compounds with acknowledged endocrine disrupting activity, mainly pesticides, remain legally or illegally in use in different countries, including Pakistan. Professional as well as public exposure to pesticides has raised cancer risk. Serum level of different endocrine disrupting pesticides has been found elevated among farmers of Pakistan [64]
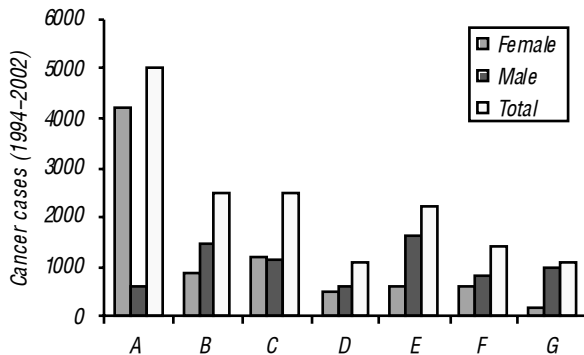


Fig. 2. Cancer cases in Punjab: breast cancer (A), cancer of digestive system (B), urogenital cancer (C), lip, oral cavity and pharynx cancer (D), lymphatics and hemopoietic cancer (E), cancer of unspecified sites (F), cancer of respiratory and intrathoracic organs (G)

and incidence of cancer in the same area has increased (Fig. 2) [65].

The extent of health hazards to agricultural workers as a result of exposure to pesticides, depends on socioeconomic and educational background of their society, the local laws governing registration, scientific and regulatory institutional setup of the country. In addition, the low educational level generally observed in rural areas, the lack of appropriate technical advice, and the lack of personal protection equipment, intensifies this scenario.

### Cancer caused by endocrine disrupting chemicals

*Breast cancer.* Breast cancer is responsible for considerable morbidity and the majority of female deaths in industrialized countries. In the etiology of breast cancer many endogenous and exogenous risk factors have

been discussed. Several studies have measured the association between blood or adipose concentrations of organochlorinated compounds (OCs), such as pesticides and PCBs, and breast cancer. Also in some studies, the women with breast cancer had higher organochlorine levels in serum as compared with controls [66]. The estrogenic effects of OCs might adversely affect breast cancer recurrence [67]. Organochlorine pesticides, including DDT, persist in human tissues for years, with correlated breast cancer incidence [68]. Beta–hexachlorocyclohexane is known to frequently accumulate in human adipose and breast tissues. An epidemiological study has indicated that exposure to beta–hexachlorocyclohexane could be one of the significant environmental risk factors for the development of human breast cancers [69]. Organophosphorous pesticides can induce more changes in this malignant breast cell line [70]. Dioxin also alters multiple endocrine systems, and its effects on the developing breast involve delayed proliferation and differentiation of the mammary gland, as well as an elongation of the window of sensitivity to potential carcinogens [71].

*Ovarian cancer.* It is proposed that the epithelial cells within the developing follicle or covering the ovarian surface, which replicate during or after each ovulation, are the cells of origin for ovarian cancer. Thus, any respite from ovulation would be protective against ovarian cancer, as supported by epidemiological results showing that the ovarian cancer risk decreases with increasing parity, combination oral contraceptive use, and lactation, at least for ovarian cancers occurring in the premenopausal age [72]. Triazine herbicides, which have shown weak estrogen and anti–androgen effects in *in vitro* studies, have been associated with 2.7–4.4–fold increase in ovarian epithelial cancer in two Italian case–control studies [73]. Moderate to high correlation between pesticides and ovarian cancer has been studied [74]. Triazine herbicides are thought to be strongly associated with ovarian cancer [75]. These results need to be replicated and the carcinogenic mechanism elucidated before drawing conclusions.

*Prostate cancer.* Prostate cancer is one of the most frequently diagnosed cancers in men and the second leading cause of cancer–related deaths in men [76]. Prostate cancer is a biologically heterogeneous tumor, with some patients suffering rapid debilitation and death and others never developing clinical manifestations of the disease [77]. Numerous epidemiological reports allude to the positive relation between pesticides and prostate cancer [78]. Morrison et al [79] in their large study, have shown that there is an exposure–response relation between herbicide exposure and prostate cancer mortality. Their data showed that mortality was related to the number of acres treated with herbicides. They have further shown that phenoxy herbicides may be responsible [79]. In two separate studies Fleming et al [80, 81] have reported that pesticide users have a higher risk of cancer than the general population, and the incidence and mortality due to prostate cancer is especially increased. It is possible that exposure to

pesticide components leads to alteration of specific biomarker profiles {i.e. her–2/neu, VEGF (vascular endothelial growth factor), UPA–r (urokinase plasminogen activator–receptor)} leading to the development of aggressive adenocarcinoma of the prostate [82].

*Testicular cancer.* Testicular cancer accounts for only about 1% of all cancers in males. It is, however, the most common tumor in males between 15 and 34 years of age [83]. Cryptorchism is one of the known risk factors for testicular cancer, suggesting that *in utero* or early postnatal exposure to estrogens or antiandrogens may contribute to development of this tumor in young men [84].

It has been proposed that endocrine disruptor chemicals may have contributed to increases in testicular cancer [85]. Some epidemiological characteristics of testicular cancer suggest a role for *in utero* estrogen exposure in the etiology of this tumor. Such a hypothesis was confirmed in a recent large case–control study in which xenoestrogen exposure during pregnancy was associated with a 4–fold increase in the risk of primary malignant germ–cell testicular cancer among residents in Ontario aged 16–59 [86]. The hypothesis that parental exposure to estrogen–mimicking pesticides could play a role in testicular cancer etiology among youngsters was tested in a large cohort study of children born from Norwegian farmers in 1952–1991 [87]. However, while higher than expected incidence of testicular cancer was observed, the excess was related to use of fertilizers, particularly for non–seminoma neoplasms. Some indication of a species–specific response of the Leydig cells of the testicular interstitium to the stimulation of the luteinizing hormone (LH), following administration of the fungicide procymidone, is provided by experimental studies in rats and mice [88]. This could account for the different sensitivity across species to the procymidone–induced Leydig cell tumorigenesis. Within species differences might be related to genetic polymorphisms, such as the overexpression of aromatase, which might result in increased estrogen production, leading to the induction of testicular cancer [89].

*Thyroid cancer.* In a very recent study, estradiol was found to modulate TSH–induced thyroid cell proliferation [90] and promote thyroid carcinogenesis. Indeed, some xenoestrogens such as organochlorine compounds [91], TCDD [92, 93], methoxychlor [94] and alachlor [95] have been shown to exert effects on the thyroid in man and experimental animals due to inhibited synthesis and increased degradation of thyroid hormones. PCBs also play an important role in the induction of thyroid adenomas [96]. As TSH is the principal hormone regulating the growth and function of the thyroid gland, any mechanism by which elevated TSH levels are achieved may be of etiologic relevance in the development of thyroid cancer. For instance, history of pregnancy, during which thyroid gland activity is increased, is associated with elevated thyroid cancer risk. Other therapeutic or environmental conditions, such as blocking thyroid hormone synthesis, administering TSH directly, an iodine–deficient diet, or environmental exposure to chemical goitrogens, including few pesticides, may also affect the thyroid function thus contributing to an increase in thyroid cancer risk. Thyroid is a frequent target for carcinogenic pesticides in experimental studies. 10% of pesticides screened for carcinogenicity by the Environmental Protection Agency, United States, produced thyroid follicular cell tumors in rodents, but mutagenicity seemed to be relevant only for acetochlor [97], and amitrole. Amitrole is metabolized to mutagenic intermediates by peroxidases, including prostaglandin synthetase, and lactoperoxidase, a model for thyroid peroxidase [98].

***Conclusions.*** The use of pesticides in agriculture is posing serious threats to the people who are directly engaged with its handling. The situation in Pakistan is at greater risks for people who are using banned chemicals and thus undergoing biomagnifications, resulting in the increased incidence of cancer among farmers and allied people. In conclusion, scientific evidence exists that endocrine disrupting pesticides adversely affect human endocrine system, while others require further investigation for a possible etiologic role in some hormone–dependent cancers. Human exposure to the broad category of pesticides should be regarded as a risk factor for hormone–dependent cancers. More sound scientific work is needed to prevent ecological and human adverse effects, including endocrine effects, resulting from improper use of pesticides or from proper use of hazardous chemicals.

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# ПЕСТИЦИДЫ С ГОРМОНОПОДОБНОЙ СТРУКТУРОЙ И ОНКОЛОГИЧЕСКИЕ ЗАБОЛЕВАНИЯ У СЕЛЬСКИХ ЖИТЕЛЕЙ ПАКИСТАНА

В обзоре рассматриваются проблемы взаимосвязи частоты развития онкологических заболеваний с производственным использованием пестицидов и химических веществ гормоноподобной структуры. В экспериментах на животных было доказано, что большинство таких пестицидов являются канцерогенами. Международное агентство по изучению рака классифицирует пестициды как канцерогенные для человека соединения. Фермеры относятся к группе повышенного риска развития острых и хронических заболеваний, развитие которых связано с действием пестицидов, однако лишь незначительное количество исследований посвящено оценке индивидуальных доз пестицидов, поступающих в организм человека. Рак молочной железы, яичника, предстательной железы, щитовидной железы и тестикулярный рак являются гормонзависимыми, в связи с чем исследуется потенциальный риск развития онкологических заболеваний, ассоциированных с производственным и экологическим воздействием пестицидам гормоноподобной структуры. Установлено, что этот риск возрастает при экспозиции пестицидам и возрастает при взаимодействии с прочими токсикантами. С другой стороны, возможная этиологическая роль органохлорных пестицидов и триазиновых гербицидов в развитии гормонзависимых онкологических заболеваний нуждается в дальнейших исследованиях.
*Ключевые слова*: рак, пестициды, пестициды гормоноподобной структуры, фермеры.