# On the need to assess cancer risk in populations environmentally and occupationally exposed to virus and chemical agents in developing countries

# Sobre a necessidade de avaliação dos riscos de câncer em populações dos países em desenvolvimento expostas ambiental e ocupacionalmente a vírus e agentes químicos

*Guilherme Franco Netto* [1,2]

[1] *Department of Biostatistics and Epidemiology, Tulane University Graduate School. 1501 Canal Street, New Orleans, LA,70112,USA.*
[2] *Fundação Nacional de Saúde. Rua Coelho e Castro 6, Saúde, Rio de Janeiro, RJ 20081-060, Brazil. guitati@rio.nutec.com.br*

**Abstract** *Evidence exists that exposure to poultry oncogenic viruses may produce elevated cancer mortality in human populations, particularly excesses of cancer of lung and excesses of cancer of lymphopoietic tissues. To date, this potential risk is unknown in populations from the developing countries. This paper suggests the need to assess cancer risk in populations of developing countries with reported environmental exposure to chicken meat products and eggs; the need to assess risk of cancer in populations inoculated with vaccines from infected chicken embryos; and the need to assess risk of cancer in occupational populations highly exposed to poultry oncogenic viruses, and with potential concurrent exposure to chemical agents known or suspected to be carcinogens.*

**Key words** *Epidemiology; Poultry; Oncogenic Viruses; Benzene; Cancer; Mortality*

**Resumo** *Existe evidência de que exposição a vírus oncogênicos de aves possa produzir elevada mortalidade de câncer em populações humanas, havendo particularmente excesso de câncer de pulmão e dos sistemas linfáticos e hemopoiéticos. Até o momento, esse risco potencial é desconhecido em populações dos países em desenvolvimento. Este manuscrito sugere a necessidade de avaliar o risco de câncer em populações dos países em desenvolvimento com sabida exposição a produtos avícolas e ovos; a necessidade de avaliar o risco de câncer em populações que foram inoculadas com vacinas desenvolvidas em embriões de aves contaminadas e a necessidade de avaliar o risco de câncer em populações de trabalhadores com grande exposição a vírus oncogênico de aves, e com potencial exposição simultânea a agentes químicos que são reconhecidos ou suspeitos carcinógenos.*

**Palavras-chave** *Epidemiologia; Aves Domésticas; Vírus Oncogênicos; Benzeno; Câncer; Mortalidade*

## Introduction

Several viruses are known carcinogens for humans. Examples are the retrovirus HTLV, which produces T-cell leukemia; Hepatitis B Heptavirinidae, which is related with hepatocellular carcinoma; Epstein-Barr Herpesviridae is associated with Burkitt's lymphoma and nasopharingeal carcinomas; and HPV Shope papillomavirus.

The Avian Leukosis and Sarcoma Virus (ALSV), the Reticuloendotheliosis Virus (REV), and Marek's Disease Virus (MDV), classified as the Poultry Oncogenic Viruses group, are well documented as cancer causing agents in chicken. They produce acute or chronic tumors of the Hematopoietic/Lymphatic Systems (HLS), endotheliomas, fibrosarcomas, cancer of the kidney, visceral lymphomas and neurolymphomatosis among several bird species (Svet-Moldavsky, 1957; Ahlstrom, 1964; Harris & Chesterman, 1964; Altaner & Svec, 1966; Simkovic, 1964; Purchase & Witter, 1986).

The prevalence of these infections is common among chicken and birds worldwide. These viruses show potential for surviving in the environment. Human exposure to these viruses occurs very often through general population contact with, and consumption of chicken/turkey meat products and eggs, exposure of the general population from inoculation with vaccines prepared from infected chicken embryos, or more intensely, by contact during occupational exposure.

Most of the existing epidemiologic data, based on farmers, veterinarians, and rural populations from the USA and Europe, have shown associations between human cancers, particularly of the lymphopoietic systems, and broad surrogates for exposure to these viruses. However, inadequate design and/or non-control of potential confounding to other known carcinogenic agents such as pesticides, fertilizers, and radiation, make it difficult to interpret these findings.

More recently, analytic epidemiologic investigations based on cohorts of workers from several job-categories from the US meat industry have consistently reported excess risk of death from multiple myeloma, leukemia, Hodgkin's Disease, non-Hodgkin's lymphoma, lung cancer, and to a lesser extent, other cancers.

Recent laboratory data has provided definitive serological evidence of human infection of ASLV and REV (Johnson, Nicholson & Durack, 1995; Johnson, Overby & Philpot, 1995; Choudat et al., 1996). These findings combined with the existing epidemiologic data suggest that Poultry Oncogenic Viruses are potentially cancinogenic for humans.

Concomitantly with refined virological and molecular studies, there is the need to conduct sound epidemiologic investigations in groups of subjects with well characterized exposure to these viruses, as chicken processing/slaughtering plant workers, in order to yield definitive conclusions whether the infectivity and the oncogenicity of Poultry Oncogenic Viruses represent a public health threat.

Besides the viral hypothesis, cancer in the meat industry may also be related to some occupational chemical exposures. Results from a mortality cohort conducted in the meat industry, including a sub-cohort of workers in the meat department from grocery stores/supermarkets, suggesting that exposure to fumes emitted from the thermal decomposition of polyvinyl chloride (PVC) during wrapping of meat may also play a role in the excesses of lung cancer and cancers of the HLS in these workers. Fumes from PVC contain chemicals known to be human carcinogens such as benzene and Polyciclic Aromatic Hydrocarbons – PAHs (Snyder et al., 1993; Aksoy, 1989; Brett et al., 1989; Hammond et al., 1976; Lloyd, 1971; Maclure & MacMahon, 1980; Mazumdar et al., 1975; Redmond et al., 1976), and phthalates which produce cancer in animals. Wrapping and labeling activities in this industry are predominantly carried out by women.

To date, the epidemiologic investigations on the role of poultry oncogenic viruses in human cancer do not include populations from developing countries.

The objective of this paper is to address the need to conduct cancer risk assessment in human populations potentially exposed to poultry oncogenic viruses in environmental and occupational populations from developing countries.

## General population exposure

Exploratory investigations have been conducted to examine the potential etiologic role of some rural/agricultural environmental factors in the explanation of the rural mortality for some relatively rare diseases, including tumors of the lymphopoietic systems. A survey was conducted among patients with leukemia and lymphoma (Rigby et al., 1965). Family clusters of these diseases were found among those with farm background. Animal leucosis viruses were considered to be one of the possible risk factors. An ecological study was conducted in Cal-

ifornia, USA (Fasal et al., 1968). The authors reported a higher risk of mortality from leukemia among both male and female farm residents when compared with the state general population. The investigators suggested that a common factor to the farm environment could be a possible explanation to the findings.

Several leukemia clusters reported since 1905 were reviewed (Aleksandrowicks, 1968). Although the author correlates human leukemia with cattle leukemia, reference was made to the role of Rous chicken tumors as a risk factor.

A case-control study was conducted based on tumor registry data in the states of New York, Maryland, and Minnesota, USA (Bross et al., 1972). The risk of dying from leukemia after having been exposed to chickens against the risk of not being exposed to chickens was statistically significant. Taking into consideration the health status of the animal, humans exposed to sick animals showed stronger association with cancer, especially in the acute leukemia series.

An ecological study was conducted on the poultry population by county for 10 southeastern states in the USA, derived from the 1964 Census of Agriculture (Piester & Mason, 1974). The human mortality rate due to cancer, by county, during the period 1950-69 was determined from information provided by the US National Center for Health Statistics. In the counties of high density of poultry population, a significant, consistent association, taking into consideration all four possible combinations between race (white and black) and sex (male and female), was observed for myeloma. Uterine and ovarian cervical cancers were excessive in high poultry population areas, but the effect disappeared when data was compared with the total US population.

The incident rates of leukemia in Olmsted County, Minnesota, USA, during the decade 1965-1974 were investigated (Linos et al., 1978). The incident rate was significantly higher among males than among females, especially in the older age groups. Rural rates were greater than the urban ones. Therapeutic radiation exposure was not taken into account. Pesticides exposure as well as animal borne virus were potential exposures discussed.

A cluster of seven cases of primary brain neoplasm in a small town was reported in the State of Missouri, USA (Morantz et al., 1985). Exposure either to a shoe factory or to a chicken hatchery were reported by patients or next-of-kin. Six of the tumors were diagnosed as glioblastoma multiform. No controls were utilized. Cases were actively searched in the town but not in the comparison groups which might bias the estimate.

A high incidence of non-Hodgkin's lymphoma over age 21 was reported in eastern Nebraska, USA (Weissenburger et al., 1986). The disease was studied in relation to corn production, total pesticides, herbicides, and insecticides county agricultural characteristics. The findings suggested that the increased incidence of non-Hodgkin's lymphoma may be related to intense agricultural activity.

Reports on high rates for non-Hodgkin's lymphoma and Hodgkin's Disease among white male residents of Hancock County, Ohio, USA, during 1960-1979 were assessed by means of a case-control study (Dubrow et al., 1988). Cause of death and usual occupation were abstracted from the death certificates. The major finding of the study shows that non-Hodgkin's lymphoma was associated with the farmer occupational group.

A case-control study was conducted in Sweden (Person et al., 1989). Occupational exposures to solvents, phenoxy acids, creosote, work as a carpenter, and contact with pets (other than dogs, cats, and birds) were associated with significantly increased risk for non-Hodgkin's lymphoma. Occupational exposure to solvents, welding, wood preservatives, phenoxy acids, and fresh wood presented significant risk factors for Hodgkin's Disease.

A population-based case-control study was conducted in an area with a high incidence of multiple myeloma with the purpose to identify and evaluate suspected environmental factors (Erickson & Karlson, 1992). Previous associations between farming and multiple myeloma were confirmed. Domestic animals and pesticides were positive indicators.

## Farming occupation reports

A case-control study was conducted in the States of Washington and Oregon, USA, using death certificates (Milhan, 1971). A significant association was found between farming occupations and death from leukemia and multiple myeloma. The association was stronger in men under age 60 with lymphatic and acute types of leukemia. Poultry farmers showed the highest proportion case excess in the leukemia series.

An investigation was conducted to assess the risk of leukemia mortality among Nebraska farmers, USA, in a matched case-control study (Blair & Thomas, 1979). Results revealed an elevated risk of leukemia among farmers, especially among farmers born after 1900 and dying

before age 66. Significantly elevated risk for farmers from heavy corn producing counties was found. When stratified by the chicken inventory, the data presented a non-significant excess risk of leukemia: Odds Ratio of 1.23 (95% CI 0.96-1.58) for the highest chicken density counties and Odds Ratio of 1.27 (95% CI 1.00-1.62) for the other chicken population counties (low and intermediate chicken density). The use of occupational data drawn from death certificates is a well known potential source of bias. The authors discussed the potential exposure from carcinogenic substances such as solvents, oils, fuels, welding fumes, herbicides, insecticides, and organic dust, as well as animal leukemic virus.

Age-adjusted mortality rates from 1971 to 1978 for white male farmers and non-farmers were computed from death certificates in Iowa, USA (Burmeister, 1981). A proportionate mortality analysis was done for the major cancer sites which presented higher cancer risk among farmers for lip, stomach, leukemia, lymphatic, multiple myeloma, and prostate.

A case-control study matched by county, age at death, and calendar year was conducted in Iowa, USA (Burmeister et al., 1982). White-male leukemia death certificates for those over age 30 who died between 1964-78 were included in the study. The overall Odds Ratio for farming and leukemia was found to be statistically significant. By the use of stratified analysis, the authors reported a statistically significant association between leukemia and acres treated with herbicides and egg-laying chickens per county. Chronic lymphatic leukemia positive findings were more consistent than unspecified lymphatic leukemia.

Another epidemiologic investigation was conducted to observe if some other types of cancer would present the same pattern as leukemia did in the previous epidemiological investigations conducted in the states of Nebraska and Iowa, USA (Burmeister et al., 1983). The aim of the study was to identify whether non-Hodgkin's lymphoma, multiple myeloma, stomach cancer, and prostate cancer mortality were associated with some farming practices, particularly insecticide exposure. White male Iowa residents who died of those diseases from 1964-78 were included in the study. Among other findings, multiple myeloma and non-Hodgkin's disease presented statistical association among the counties with high egg-laying chicken activities. The authors suggested further investigation on the potential role of Marek's disease be taken in account as a possible etiologic factor.

Data on occupational and family history were collected in a population-based incidence case-control study in Tasmania, Australia, in order to assess myeloproliferative and lymphoproliferative disorders specific risks, and to explore possible common etiologies (Giles et al., 1984). Among farmers, a statistically significant Odds Ratio was found for the overall disease-group, but no important differences were found between the specific type of diagnosis and the time of employment (ever or more than five years). Viruses, chemicals, and ionizing radiation are the three broad types of environmental agents thought to be etiologically related with myeloploriferative and lymphoproliferative disorders.

A case-control study among white male residents in the state of Wisconsin, USA, was conducted (Cantor & Blair, 1984). The aims of the investigation were to test the hypothesis whether farmers would have elevated risk of multiple myeloma, and if so, to investigate which agricultural factors might be related to the disease. The crude Odds Ratio showed a significant association. Taking into account year of birth, the association between high chicken inventory and multiple myeloma is significant in the group born between 1897-1905, whereas the insecticide use by acreage is significant in the group born between 1906-1945. The main limitations of the study are the use of death certificates as the source for occupation, which may be inaccurate, and the cause of death, which may not be confirmed.

A Proportional Mortality Ratio (PMR) analysis among 28,032 male farmers, aged 20 years or more who have died between 1950-78 was conducted in British Columbia, Canada (Gallagher et al., 1984). Cancer excess were found from stomach, lip, and leukemia. A new finding was the excess risk for aplastic anemia, not statistically significant, among the deaths from the 1950-59 period.

A PMR analysis was conducted in North Carolina, USA, (Delzell & Grufferman, 1985) reporting for the first time non-white data in this review series. Excesses for both race subgroups were found for tuberculosis, disease of the skin and subcutaneous tissue, and external causes. Prostate cancer was in excess among those deceased under 65 years of age. White farmers had an excess of melanoma, and other skin cancer. Non-white farmers had an excess of melanoma, brain cancer, and leukemia. Leukemia excess among non-white farmers was predominant among those born in 1900 or before. Taking in consideration county poultry activity, excess risk of leukemia was observed among the non-white male farmers.

A case-control study was reported (Schumacher, 1985) based on data from cancer registry from the state of Utah, USA. Cases were defined as white males aged 35 years or older with a non-Hodgkin's lymphoma who died during the 1967-82 period. Stratified analysis was done taking into account farmers and non-farmers occupation, age-category, and date of birth. A significantly high risk for non-Hodgkin's lymphoma was found for farmers whose diagnoses were made during the years 1952-71, but not for those diagnosed after 1977. Lymphocityc lymphoma was the major diagnosis cell type.

Findings from a New Zealand Cancer-registry based case-control study involving male leukemia patients registered during 1979-1983, aged 20 years or more at time of registration were reported (Pearce et al., 1987). Agriculture/forestry/fishing workers category presented the most significant excess, when compared with the other labor categories. More detailed analysis of the occupations from the agriculture/forestry/fishing category show a statistical significant excess of leukemia among the livestock farm group. No cases were identified among the poultry farm workers.

In the New Zealand non-Hodgkin's lymphoma excess (Pearce et al., 1986), it was found that agricultural workers were at increased risk of developing malignant lymphoma. Similar excesses have been found in studies in other countries. Some of these studies found an association between malignant lymphoma and exposure to phenixyl herbicides or chlorophenols.

As an update of the previous study, (Pearce et al., 1987), interviews were conducted with patients from the non-Hodgkin's lymphoma other than lymphosarcoma and reticulosarcoma group. Data from the interviews were negative for any association between insecticides and the diseases. However, it was suggested that the overall excess risk for farmers was attributable to excess among farmers who had carried out fencing work or been employed in a meat processing work. The authors discussed the need for considering the potential role of zoonotic oncogenic virus in the etiology of malignant lymphoma among exposed people and workers. It was pointed out the fact that epidemiological evidence for the role of zoonotic oncogenic viruses is weak. Most studies have been ecological in nature and have not included serological test for evidence of viral infection. However, it is not clear whether such test would be informative without more adequate knowledge of the possible mechanisms of infection. It had been suggested that these viruses may cause tumors in animals without serological evidence of viral infection.

A proportionate mortality analysis (PMR; Proportional Cancer Mortality Ratio – PCMR) of Wisconsin white male farmers, aged 18 and over, who died during the years 1968-1976 was conducted (Saftlas et al., 1987). Cancer sites with significantly elevated PMRs included stomach, prostate, eye, Hodgkin's lymphoma, leukemia, lymphosarcoma and reticulosarcoma, and other lymphomas. For each major agricultural activity, three hierarchic levels of intensity were categorized. Although cancer excess risk was found for some exposure categories, mainly herbicides, insecticides, and fertilizer, no association was found for the chicken agricultural exposure category.

Other investigators (Cuzick & De Stavolta, 1988) studied multiple myeloma risk factors by means of an exploratory case-control study. Although multiple myeloma is reported to be increasing in most parts of the world, very little is known about its etiology. Farming and agriculture, radiation, and a variety of chemicals (asbestos, arsenic, cutting oils, heavy metals, petrochemicals, and materials associated with plastic and rubber manufacture) which are suspected agents, but none of these observations are unequivocal. Increased risk in leather workers and woodworkers have also been reported. Immunesupression is postulated to be important, possibly resulting from chronic antigenic stimulation. Some iatrogenic factors are also mentioned as etiologic. The study was conducted in England and Wales between 1978 and 1984. Risk factors studied included occupation, chemical exposure, radiation exposure, prior disease, immunizations, chronic infections and markers for defects in immune regulations. Significant risk with agriculture and food processing was observed, but could not be broken down to those exposed to animals/meat products or those exposed to pesticides. Significant excesses were also noted for reported exposures to chemicals and gases/fumes.

The risk of malignant lymphoma after potential exposure to phenoxy acid herbicides was studied (Wilklund et al., 1988) in a Sweden historical follow-up study based on occupational information from the 1960 national census. All those employed in the agriculture or forestry at that time were followed up in the Cancer-Environment Register between 1961-1979. Non-Hodgkin's lymphoma did not show any increase in the cohort or subcohorts. Hodgkin's disease was found to be statistically significant among fur farming and silviculture.

A death certificate-based case control study was performed (Schumacher & Deizell, 1988) to investigate associations between occupation and Non-Hodgink's lymphoma in North Carolina, USA. Cases consisted of men who died of NHL during the years 1968-70, 1975-77, and 1980-82. Occupation and industry were obtained from the death certificates. No association was found between NHL and farming employment.

Based on the excess risks of lymphomas, leukemia, and multiple myeloma reported in agricultural workers, a case-control study was conducted (Brownson & Reif, 1988). Cases and controls were identified through the State of Missouri Department of Health. Cases had to be 20 years or older during 1984 and 1985. A significant excess among farmers was found for acute lymphatic leukemia among those who died younger than 65 years, and reticulosarcoma among those aged 65 or older.

The problem of multiple exposures among agricultural workers was discussed (Pearce & Reif, 1990). The investigators pointed out that several limitations existed in the current epidemiological knowledge on populations potentially exposed to agricultural chemicals, such as pesticides, herbicides, and animal viruses that are potential human carcinogens.

Occupations in agriculture in Denmark that show a high risk for cancer of the lymphopoietic system, Hodgkin's disease, leukemia, and multiple myeloma, are among those who entail contact with animals (Ronco et al., 1992).

In a study aimed to evaluate agricultural factors and the risk of multiple myeloma in eastern Nebraska, USA, (Zahm & Weisenburger, 1992), an increased risk was found among women who had ever lived or worked on a farm, and who had ever used insecticides or herbicides on the farm, when compared with men. Also, a study of farmers from 23 American states shows that this difference is particularly strong in the central USA, which is heavily agricultural.

A statistically significant high malignant melanoma excess among California veterinarians was reported (Fasal et al., 1966).

The causes of death among 1,551 white male veterinarians who died from 1966 through 1977 was compared with the US general population through a proportionate mortality study (Blair & Hayes, 1980). Mortality was significantly increased for leukemia and Hodgkin's disease as well as certain other types of cancer: cancer of skin, and cancer of brain and central nervous system. Mortality from leukemia and Hodgkin's disease was statistically significant among practicing veterinarians but not for the non-practitioner. Potential exposures to pesticide, ionizing radiation (due to lack of safety in the use of X-rays equipment), and zoonotic animal viruses were discussed, although not statistically tested, as the possible etiologic factors to explain their findings.

Veterinarians mortality was studied by means of a cohort study in Missouri, USA (Boots et al., 1966). No significant cancer excess were reported.

The mortality of 20.000 veterinarians was studied (Matanoski & Lilienfield, 1976). Statistically significant Standardized Mortality Ratio (SMR) excesses were found for cancer of the large intestine, prostate, brain, lymphatic tissue when compared with the US general population.

Higher overall death rates among Illinois veterinarians was reported when compared with the US general Population (Schnurrenberger et al., 1977).

However. recent investigations on cancer among veterinarians did not show excess (Linken, 1983; Miller & Beaumont, 1995).

## Discussion

The investigations described above are anecdotal reports, ecologic correlation, cross sectional surveys, registry-based case-control, and proportionate mortality studies which generated some hypotheses in the role of certain environmental/occupational exposure and the observation of cancer excess.

However, definite causal association cannot be drawn from those findings. The major limitations of such epidemiologic study designs are 1) the inaccurate exposure assessment which is often associated with misclassification of exposure bias; 2) the potential lack of accuracy from the reported underlined cause of death for some groups of diseases in the death certificate, may be another source of bias; and 3) lack of control for confounding effects from existing agents in the environment under appreciation, such as insecticides and radiation.

Nevertheless, the conduct of ecologic investigations may be helpful to explore the role of exposure to poultry oncogenic virus as a potential cancer risk factor in populations from developing countries. Mortality databases, Cancer Registry databases, and Death Certificates are examples of the needed sources of information to be used as the numerator of the estimate. General Populations, Regional Populations, Local Populations, Total Mortality, All

Cancers Mortality are the requested data to be used as the denominator of the estimate of interest. It is recommended to adjust the estimate by sex and by age group.

Proportional mortality ratio can be conducted when the mortality set of a population with known exposure is available. Thus, the proportion of cause-specific deaths of interest in the study population can be contrasted with the proportion of the corresponding cause-specific deaths in the general population.

## Exposure through vaccine inoculation

The use of chicken embryos in the production of yellow fever vaccine during the World War II suggested the presence of viruses capable of inducing neoplasm in avian species. A case-control mortality study among army veterans was conducted (Walter, 1972) to determine whether the vaccine could also produce cancer in man in relation to their immunization status against yellow fever during military service. The Yellow Fever Vaccination did not show any evidence of cancer excess in that investigation.

### Discussion

The populations from the developing world may be potentially highly exposed to vaccines prepared from chicken embryos and eggs infected with the poultry oncogenic viruses. It would be of public health interest to characterize the source and the types of vaccines that may be infected, and the magnitude of the potential exposure. Also, analytic epidemiologic investigations, as case-control studies, would be suitable to investigate whether there is a suggestive relationship between inoculation of infected vaccine and cancer excess. Case-control studies report the odds ratio, i.e., the odds of being a case taking in account the exposure of interest, and the odds of not being a case taking in account the exposure of interest.

## Meat industry workers reports

### Exposure characterization

Workers in the Meat Industry are highly exposed to zoonotic oncogenic viruses through the slaughtering/processing industrial activity. However, those workers may be exposed to certain chemical agents when PVC-wrapping takes place. PVC film was introduced in 1963 and still is the major fresh meat packaging material currently in use (Vandervolt & Brooks, 1977). The amount of plastic melted or combusted varies considerably according to worker experience and use of protective material, and concentration of contaminants varies directly with the operating temperature of the wire (Smith et al., 1983). PVC-wrapping fumes contain chemical agents that are known human and/or animal carcinogenic i.e., benzene, polycyclic aromatic hydrocarbons, and phthalates.

### Preliminary findings

Findings from England (Proportionate Mortality Ratio-PMR), Denmark (Standardized Mortality Ratio-SMR), and Sweden (Standardized Incident Ratio-SIR) suggested excesses of lung cancer among butchers (Fox et al., 1982) in the period between 1961 and 1973. A similar excess was identified for the 1959-63 period in England and Wales (Griffit, 1982). A similar excess was found in Germany for the period 1954-66 (Doerken & Rehpenning, 1982). Hand viral warts are often found among butchers by dermatologists. The warts may produce malign change and a tentative assumption was made on their role to explain lung cancer excess (Pegum, 1982).

A PMR analysis from the state of Washington, USA, was presented (Milhan, 1982), suggesting no lung cancer excess among butchers and meatcutters.

A mortality excess of tumor of the hematopoyetic/lymphatic systems and tumor of connective tissues were reported in a PMR investigation among male cattle and poultry slaughterhouse workers from Baltimore, Maryland, USA (Johnson & Fishman, 1982). The authors also observed excess mortality of cancer of trachea, bronchus, and lung, and cancer of the bladder.

The relationship between occupational butcher exposure and lung cancer while controlling for cigarette smoking by means of a reanalysis of a previous case-control study conducted in the 60's was reported (Vena et al., 1982). Cases were patients admitted to a hospital in Buffalo, New York, USA. The excess risk was accounted for by cigarette smoking.

An update of the previous SMR analysis carried out in Denmark during the period 1961-73 was conducted (Lynge et al., 1983), including now the years from 1975-80. Lung cancer excess risk was confirmed among butchers in that country. A questionnaire was administrated to a representative random sample of male slaughterhouse workers in order to assess type of work and smoking habits. There were minor variations between smoking habits

among the job-categories. The lung cancer SMR for the skilled workers, who had worked an average of 20 years in slaughterhouse were in excess, whereas the lung cancer SMR for the non-skilled who had worked an average of 10 years in similar work environment, did not showed the same effect.

## Occupational cohorts

A historical cohort mortality study among meat industry workers was conducted (Johnson et al., 1986a) aimed to better clarify whether a population highly exposed to many of these exposures would present positive findings using both PMR and SMR analysis. The study population was selected from members of a meatcutter's union in the city of Baltimore, State of Maryland, USA. 28,901 persons were followed up within the period from 1949 to 1979. To date, the Baltimore meatcutter's union cohort is the most thorough epidemiologic investigation on the association of zoonotic oncogenic viruses exposure with human mortality.

The investigators initially reported the result from the white male sub-population. Ninety five percent of this group had worked in only one job-category lifetime, allowing for an separate data analysis by each job-category. The expected number of cases were drawn from the Baltimore general population rates. For the entire cohort, statistically significant excess was identified for all cancers, cancer of the buccal cavity and pharynx, cancer of large intestine, and lung cancer. Among the 36 observed deaths from the Chicken-Slaughtering workers, the overall cancer SMR was 0.69. No deaths from hematopoyetic/lymphatic tumors were observed. Cancer of Buccal Cavity, Cancer of Esophagus, and Cancer of Stomach excesses were based in only one observed death each. Workers from Meat Departments of Grocery Stores/Supermarkets who also manipulate chicken and fowl did not present any statistically significant excess cancer risk, except with lung cancer when the lost of follow up were withdrawn from the analysis since their last contact, 46 observed deaths, 33.92 expected deaths, SMR 1.36, 95%CI (0.99; 1.81), $\chi^2$ 3.95.

The same investigators (Johnson et al., 1986b) presented new data from a sub-cohort from the Baltimore meatcutter's union study previously described. It was the first analyses on the mortality experience of women who work in the meat industry. Considerations of specific type of exposures were made. Women in the Meat Industry traditionally have been wrapping and labeling meat as a predominant task. The wrapping fumes contain chemical agents that are known human and/or animal carcinogenic i.e., benzene, polycyclic aromatic hydrocarbons, and phthalates. Those workers are also exposed to viruses that naturally cause leukemia and lymphosarcoma in animals. Exposure to nitrosamines, a known carcinogen, is another potential source of exposure among them.

Among the 484 Chicken Slaughtering workers, there were 21 observed deaths. Lung cancer presented statistically significant excess risk, 3 observed deaths, SMR 4.56. No deaths were observed in the hematopoyetic/lymphatic systems.

The 3622 Grocery Stores/Supermarket white women workers presented excess for all cancers of the hematopoyetic/lymphatic systems based in 10 observed deaths (PMR 2.17, statistically significant). The specific cancer sites excess were Hodgkin's Lymphoma, 1 observed death, SMR 1.23; Leukemia & Aleukemia, 4 observed deaths, SMR 1.85; and Cancer of All Other Lymphopoietic Tissues, 3 observed deaths, SMR 2.46. Cancer of lung was also found in excess based on 14 deaths, SMR 1.95, was statistically significant.

The mortality rate among nonwhite men sub-cohort from the same Baltimore meatcutter's union study was reported (Johnson, 1989). Statistically significant excess for lung cancer among workers in abattoirs, and esophagus cancer among workers in meatpacking plants were found. No excesses occurred among workers from Chicken-Slaughtering.

A nested case-control study was conducted (Johnson, 1991) to investigate whether job-related tasks were associated with the lung cancer excess in the Baltimore meatcutter's follow-up investigation, and whether tobacco smoking could explain the findings. Exposure to live animals and employment in the kill/dress area were identified as factors associated with the greatest risk of lung cancer. Workers in meatpacking plants and meat departments of supermarkets were at a higher risk of lung cancer than workers in non-meat industries. Lung cancer was not explained by cigarette smoking. In a update of the Baltimore meatwrapper's union investigation (Johnson, 1994) it was found lung cancer excess among women, SMR 1.6 (95% CI 1.1-2.2); PMR 1.5 (95% CI 1.0-2.0). For men, the SMR for cancer of the buccal cavity and pharynx was 1.8 (95% CI 1.0-3.0), and for colon cancer it was 1.5 (95% CI 1.1-2.1). The respective PMRs were 1.9(95% CI 1.1-3.1) and 1.5(95% CI 1.1-2.1). Lung cancer excess among women is discussed based on the evidence that

wrapping and labeling in the meat industry has been historically done by women, and the role of its fumes as a potential etiologic factor need further investigation.

The findings after an additional 9-year follow-up of the previously studied group of workers in abattoirs and workers in meat-packing plants was reported (Johnson, 1995). Excess risk was found for all cancer combined, cancers of the lung, buccal cavity and pharynx, esophagus, colon, bladder kidney, and bone. Of relevant interest is the identification of a four-fold significant risk of lung cancer among white-women whose predominant activity in the meat industry is the wrapping, labeling, and packing of meat. In summary, lung cancer mortality in the meat industry is statistically relevant in the physical areas where killing/dressing, smoking and curing of meat, and wrapping/labeling activities took place.

The mortality of the sub-cohort of poultry slaughtering/processing workers from the Baltimore meatcutter's cohort was investigated (Johnson et al., 1997). The investigators found statistically significant excesses of risk to cancer of the esophagus, liver, pancreas, and tumors of the lymphopoietic systems, as a group. Interestingly, there is a non-significant excess of cancer of lung in the white males, and in white females.

Another nested case-control study was conducted in the Baltimore meatcutter's cohort in order to assess the relationship between occupational exposure and death from tumors of the lymphopoietic systems. Slaughtering activities involving heavy exposure to oncogenic viruses were strongly associated with lymphopoietic tumors, especially with lymphomas. Workers in chicken slaughtering/processing plants presented an odds ratio of 2.8, 95% CI (0.8-9.5). Among the supermarket workers, wrapping meat was associated with increased risk of cancer of lymphopoietic tissues, OR 3.8, 95% CI (1.0-14.3). Also, meatcutting in supermarkets was associated with multiple myeloma in males, OR 18; 95% (CI 1.6-207.5).

There are reports of analytical epidemiologic investigations in workers from the meat industry other than the Baltimore meatwrapper's cohort. A follow-up study carried out in England (Coggon et al., 1989) reported statistically significant lung cancer excess risk among butcher workers. The excess was greatest among those with ten or more years of exposure and interestingly, on those workers exposed to recently slaughtered meat (warm meat). Tobacco effect was not controlled. A historical cohort was conducted in Geneva, Switzerland, (Guberan et al., 1993) among all self employed butchers born since 1880 who set up a shop from 1901 to 1969, and their wives. The study group was followed up from 1901 to 1990 for general mortality, from 1942 to 1990 for cause specific mortality, and from 1970 to 1989 for incidence of cancer. Among cancers, there were significant excesses in the incidence and mortality from colorectal cancer, cancer of the prostate, and in incidences of liver cancer. The risk of lung cancer was increased for pork butchers. A cluster of deaths of leukemia was identified among older butchers, who were born last century. Of interest is the observation that the cases of leukemia are related to persons who slaughtered animals, task performed by butchers until 1949.

Most recently, we found cancer excess in a historical cohort of 7,700 workers from poultry slaughtering/processing plants in Missouri, USA (Netto & Johnson, 1998, in press). Cancer of bronchus, trachea & lung and cancer of kidney presented statistically significant excess. A positive dose response relationship was found for cancer of bronchus, trachea & lung, and cancer of the kidney by means of latency and duration of employment analysis. To a lesser extent, some cancers of the lymphopoietic system were also found excessive: Lymphosarcoma & Reticulosarcoma, Leukemia & Aleukemia, and Cancer of All Other Lymphopoietic Tissues. Several other cancers were also excessive, such as cancer of stomach, cancer of large intestine, cancer of pancreas, cancer of bladder, cancer of cervix, cancer of thyroid, and cancer of central nervous system.

## Discussion

The findings from the several investigations in meat industry cohorts have shown that there is a suggestive relationship between occupational exposure in the chicken slaughtering/processing industry and cancer excess, particularly of lung cancer and cancer of lymphopoietic tissues.

Analytic epidemiologic investigations in workers from the poultry industry in the developing countries should be considered, in order to help to elucidate whether their occupational populations who are highly exposed to poultry oncogenic viruses also present cancer risk excess, particularly cancer of lungs and cancer of lymphopoietic systems.

The major advantage of cohort study designs is the unique opportunity to quantify the amount of time since exposure (usually by means of person-years) in a well characterized

population. The estimate often used in retrospective, or historical cohorts, is the standardized mortality ratio – SMR. The SMR statistics is a cause-specific mortality rate in the study population (numerator) contrasted with the respective mortality rate in a comparison population (denominator).

The possibility to conduct historical cohorts will depend on the availability of exposure records, and reliable information on the workers vital status through the closing date of the follow-up. Also, in order to compute the SMR, mortality rates from the comparison population, adjusted by age groups and calendar periods need to be available. Given that the suspected cancers are relatively rare events, the power of the prospective investigations must be considered. Furthermore, depending on the characteristics of the chicken industrial process in developing countries, there is the need to assess the role of potential concurrent chemical exposure in cancer risk.

## Conclusions

A thorough review of the published works on the putative relationship between poultry oncogenic viruses and cancer mortality is presented. The majority of the available data was drawn from epidemiologic investigations conducted on populations in the US and Europe. Although inconclusively, the literature suggests that the poultry oncogenic viruses may be a risk factor of cancer for the human populations. Cancer of Bronchus, Trachea & Lung, and Cancer of Lymphopoietic Systems have been consistently found in excess.

The intensity of exposure to poultry oncogenic viruses in the general population of the developing countries may be quite different to that currently observed in the developed countries. This paper addresses the public health relevance to investigate whether the populations from the developing countries would present similar risk.

Questions to be answered are: 1) whether populations from developing countries, particularly those from rural areas, experience higher intensity of exposure than the corresponding populations of the developed countries; 2) whether the populations from developing countries have higher exposure to vaccines infected with the poultry oncogenic viruses; and 3) whether the occupational exposure to poultry oncogenic viruses in the developing countries is currently higher than that from the developed countries.

## References

AHLSTROM, C. G., 1964. Neoplasm in mammals induced by Rous chicken sarcoma material. *National Cancer Institute Monographs*, 17:299-319.

ALEKSANDROWICKS, J., 1968. Leukemic in humans and animals in the light of epidemiologic studies with reference to problems of its prevention. *Acta Medica Polona*, 9:217-230.

AKSOY, M., 1989. Hematotoxicity and carcinogenicity of benzene. *Environmental Health Perspectives*, 82:193-197.

ALTANER, C. & SVEC, F., 1966. Virus production in rat tumors induced by chicken sarcoma virus. *Journal of the National Cancer Institute*, 37:745-752.

BLAIR, A. & HAYES, M. J., 1980. Cancer and other causes of death among US veterinarians, 1966-1977. *International Journal of Cancer*, 25:181-185.

BLAIR, A. & THOMAS, T. L., 1979. Leukemia among Nebraska farmers: a death certificate study. *American Journal of Epidemiology*, 110:264-273.

BOOTS, R. P.; EDLAVITCH, S. & PAYNE, G., 1966. Mortality of Missouri veterinarians. *Journal of the American Veterinary Medical Association*, 149: 499-504.

BRETT, S. M.; RODRICKS, J. V. & CHINCHILLI, V. M., 1989. Review and update of leukemia risk potential associated with occupational exposure to benzene. *Environmental Health Perspectives*, 82: 267-281.

BROSS, I. D. J.; BERTELL, R. & GIBSON, R., 1972. Pets and adult leukemia. *American Journal of Public Health*, 62:1520-1531.

BROWNSON, R. C., & REIF, J. S., 1988. A cancer registry-based study of occupational risk for lymphoma, multiple myeloma and leukemia. *International Journal of Epidemiology*, 17:27-32.

BURMEISTER, L. F., 1981. Cancer mortality in Iowa farmers, 1971-1978. *Journal of the National Cancer Institute*, 66:461-464.

BURMEISTER, L. F.; VAN LIER, S. F. & ISACSON, P., 1982. Leukemia and farm practices in Iowa. *American Journal of Epidemiology*, 155:720-728.

BURMEISTER, L. F.; EVERETT, G. D.; VAN LIER, S. & ISACSON, P., 1983. Selected cancer mortality and farm practice in Iowa. *American Journal of Epidemiology*, 118:72-77.

CANTOR, K. P. & BLAIR, A., 1984. Farming and mortality from multiple myeloma: a case-control study with the use of death certificates. *Journal of the National Cancer Institute*, 72:251-254.

CHOUDAT, D.; DAMBRINE, G.; DELEMOTTE, B. & COUDERT, F., 1996. Occupational Exposure to poultry and prevalence of antibodies against Marek's disease virus and avian leukosis retroviruses. *Occupational and Environmental Medicine*, 53:403-10.

COGGON, D.; PANNET, B.; PIPPARD, E. C. & WINTER, P. D., 1989. Lung cancer in the meat industry. *British Journal of Industrial Medicine*, 46:188-191.

CUZICK, J. & DE STAVOLTA, B. 1988. Multiple myeloma – A case-control study. *British Journal of Cancer*, 57:516-520.

DELZELL, E. & GRUFFERMAN, S., 1985. Mortality among white and nonwhite farmers in North Carolina, 1976-1978. *American Journal of Epidemiology*, 121:391-402.

DOERKEN, H. & REHPENNING, W., 1982. Lung cancer in butchers. *Lancet*, 3:561.

DUBROW, R.; PAULSON, J. O. & WINDIAN, R. W., 1988. Farming and malignant lymphoma in Hancock County, Ohio. *British Journal of Industrial Medicine*, 45:25-28.

ERICKSON, M. & KARLSON, M., 1992. Occupational and other environmental factors and multiple myeloma: a population based case-control study. *British Journal of Industrial Medicine*, 49:95-103.

FASAL, E.; JACKSON, E. W. & KLAUBER, M. R., 1966. Mortality in California veterinarians. *Journal of Chronic Diseases*, 19:293-306.

FASAL, E.; JACKSON, E. W. & KLAUBER, M. R., 1968. Leukemia & lymphoma mortality and farm residence. *American Journal of Epidemiology*, 87: 267-274.

FOX, A. J.; LYNGE, E. & MALKER, H., 1982. Lung cancer in butchers. *Lancet*, 1:165-166.

GALLAGHER, R. P.; THRELFALL, W. J.; JEFFRIES, E.; BAND, P. R.; SPINELLI, J. & COLDMAN, A. J., 1984. Cancer and aplastic anemia in British Columbia farmers. *Journal of the National Cancer Institute*, 72:1311-1315.

GILES, G. G.; LICKISS, J. N.; BALKIE, M. J.; LOWENTHAL, R. M. & PANTON, J., 1984. Myeloproliferative and lymphoproliferative disorders in Tasmania, 1972-80: Occupational and familial aspects. *Journal of the National Cancer Institute*, 72:1233-1240.

GRIFFIT, G. W., 1982. Lung cancer in butcher. *Lancet*, 2:39.

GUBERAN, E.; USEL, M.; RAYMOND, L. & FIORETTA, G., 1993. Mortality and incidence of cancer among a cohort of self employed butchers fro Geneva and their wives. *British Journal of Industrial Medicine*, 50:1008-1016.

HAMMOND, E. D.; SELIKOFF, I. J. & LAWTHER, P. O., 1976. Inhalation of B[a]P and cancer in man. *Annals of the New York Academy of Sciences*, 271: 116-124.

HARRIS, R. J. C. & CHESTERMAN, F. C., 1964. Growth of Rous sarcoma in rarts, ferrets, and hamsters. *National Cancer Institute Monographs*; 17:321-335.

JOHNSON, E. S., 1989. Mortality among nonwhite men in the meat industry. *Journal of Occupational Medicine*, 31:270-272.

JOHNSON, E. S., 1991. Nested case-control study of lung cancer in the meat industry. *Journal of the National Cancer Institute*, 83:1337-1339.

JOHNSON, E. S., 1994. Cancer mortality among workers in the meat department of supermarkets. *Occupational and Environmental Medicine*, 51:541-547.

JOHNSON, E. S. & FISHMAN, H. R., 1982. Cancer mortality among butchers and slaughtehouse workers. *Lancet*, 1:913-914.

JOHNSON, E. S.; FISHMAN, H. R.; MATANOSKI, G. M. & DIAMOND, E., 1986a. Cancer mortality among white males in the meat industry. *Journal of Occupational Medicine*, 28:23-32.

JOHNSON, E. S.; FISHMAN, H. R.; MATANOSKI, G. M. & DIAMOND, E., 1986b. Occurrence of cancer in women in the meat industry. *British Journal of Industrial Medicine*, 43:597-604.

JOHNSON, E. S.; DALMAS, D.; NOSS, J. & MATANOSKI, G. M., 1995. Cancer mortality among workers in abbatoirs and meatpacking plants: an update. *American Journal of Industrial Medicine*, 27:389-403.

JOHNSON, E. S.; NICHOLSON, L. G. & DURACK, D. T., 1995. Detection of antibodies to avian leukosis/sarcoma viruses (ALSV) and reticuloendhoteliosis viruses (REV) in humans by ELISA. *Cancer Detection and Prevention*, 19:394-404.

JOHNSON, E. S.; OVERBY, L. & PHILPOT, R., 1995. Detection of antibodies to avian leukosis/sarcoma viruses and reticuloendhoteliosis viruses in humans by Western Blot Assay. *Cancer Detection and Prevention*, 19:472-486.

JOHNSON, E. S.; SHORTER, C.; RIDER, B. & JILES, R., 1997. Mortality from cancer and other diseases in poultry slaughtering/processing plants. *International Journal of Epidemiology*, 26:1142-50.

LINKEN, L. J., 1983. Mortality among British veterinarian surgeons. *British Medical Journal*, 287: 1017-19.

LINOS, A.; KYLE, R. A.; EVEBACK, L. R. & KURLAND, L. T., 1978. Leukemia in Olmsted County, Minessota, 1965-1974. *Mayo Clinic Proceedings*, 53:714-718.

LLOYD, J. W., 1971. Long term mortality study of steelworkers: V. Respiratory cancer in coke plant workers. *Journal of Occupational Medicine*, 13: 53-68.

LYNGE, E.; ANDERSEN, O. & KRISTENSEN, T. S. L., 1983. Lung cancer in danish butchers. *Lancet*, 1:527-528.

MACLURE, K. M. & MACMAHON, B., 1980. An epidemiologic perspective of environmental carcinogenesis. *Epidemiologic Reviews*, 2:19-48.

MATANOSKI, G. M. & LILIENFELD, A., 1976. How veterinarians die. Presented at the *194th Meeting of the American Public Health Association*. Miami

Beach: American Public Health Association.

MAZUMDAR, S.; REDMOND, C. K. & SOLLECITO, W., 1975. An epidemiologic study of exposure to coal tar pitch volatiles among coke oven workers. *Journal of the Air Pollution Control Association*, 25:382-389.

MILLER, J. M. & BEAUMONT, J. J., 1995. Suicide, cancer and other causes of death among California veterinarians, 1960-1992. *American Journal of Internal Medicine*; 27:37-49.

MILHAN, S., 1971. Leukemia and multiple myeloma in farmers. *American Journal of Epidemiology*, 94: 307-310.

MILHAM, S., 1982. Lung cancer in butchers. *Lancet*, 1:690.

MORANTZ, R. A.; NEUBERGER, J. S.; BAKER, L. H.; BERINGER, G. B.; KAUFMAN, A. B. & CHIN, T. D. Y., 1985. Epidemiological findings in a brain-tumor cluster in Western Missouri. *Journal of Neurosurgery*, 62:856-860.

NETTO, G. F. & JOHNSON, E. S., 1998. *Mortality in the Chicken Processing/Slaughtering Industry in Missouri,USA*. New Orleans: Tulane University Graduate School (in press).

PEARCE, N. E.; RAEWYN, A. S.; HOWARD, J. K.; FRASER, J. & LILLEY, B. M., 1986. Leukemia among New Zealand agricultural Workers. *American Journal of Epidemiology*, 124:402-409.

PEARCE, N. E.; SHEPPARD, R. A.; SMITH, A. H. & TEAGUE, C. A., 1987. Non-Hodgkin's Lymphoma and farming: an expanded case-control study. *International Journal of Cancer*, 39:155-161.

PEARCE, N. & REIF, J. S., 1990. Epidemiological studies of cancer in agricultural workers. *American Journal of Industrial Medicine*, 18: 133-148.

PEGUM, J. S., 1982. Lung cancer in butchers. *Lancet*, 3:561.

PERSON, B.; DAHLANDER, A.-M.; FREDRIKSSON, M.; BRAGE, H. N.; OHLSON, C.-G. & AXELSON, O., 1989. Malignant lymphomas and occupational exposures. *British Journal of Industrial Medicine*, 46:516-520.

PIESTER, W. A. & MASON, T. J., 1974. Human cancer mortality in relation to poultry population, by county, in 10 Southearstern States. *Journal of the National Cancer Institute*, 53:45-49.

PURCHASE, H. G. & WITTER, R. L., 1986. Public health concerns from human exposure to oncogenic avian herpesvirus. *Journal of the American Veterinary Medical Association*, 189:1430-36.

REDMOND, E.; STROBINO, B. & CYPRESS, R., 1976. Cancer experience among coke by-products workers. *Annals of the New York Academy of Sciences*, 27:102-115.

RIGBY, G.; ROSENLOF, R. C. & PRATT, P., 1965. Rural leukemia and lymphoma. *Proceedings of the American Association for Cancer Research*, 6:54.

RONCO, G.; COSTA, G. & LYNGE, E., 1992. Cancer risk among Danish and Italians farmers. *British Journal of Industrial Medicine*, 49:220-225.

SAFTLAS, A. F.; BLAIR, A.; CANTOR, K. P.; HANRAHAN, L. & ANDERSON, H. A., 1987. Cancer and other causes of death among Wisconsin farmers. *American Journal of Industrial Medicine*, 11:119-129.

SCHUMACHER, M. C., 1985. Farming occupations and mortality from Non-Hodgkin's Lymphoma in Utah. *Journal of Occupational Medicine*, 27:580-584.

SCHUMACHER, M. C. & DEIZELL, E. A, 1988. Death certificate case-control study of Non-Hodgkin's Lymphoma and occupation in men in North Carolina. *American Journal of Industrial Medicine*, 13:317-330.

SCHNURREMBERGER, P. R.; MARTIN, R. J. & WALKER, J. F., 1977. Mortatity in Illinois veterinarians. *Journal of the American Veterenary Medical Association*, 170:1071-1075.

SIMKOVIC, D., 1964. Interaction betweeen mammalian tumor cels induced by Rous virus and chicken cells. International Conference on Avian Tumor Viruses. *National Cancer Institute Monographs*, 17:351-364.

SMITH, T. J.; CAFFARELA, J. J. & CHELTON, C., 1983. Evaluation of emission from simulated commercial meat wrapping operation using PVC wrap. *American Industrial Hygiene Association Journal*, 44:176-83.

SNYDER, R.; WITZ, G. & GOLDSTEIN, B. D., 1993. The toxicity of benzene. *Environmental Health Perspectives*, 100:293-306.

SVET-MOLDAVSKY, G. J., 1957. Development of multiple cysts and of haemorragic affections of internal organs in albino rats treated during the embryonic or newborn period with Rous sarcoma virus. *Nature*, 180:1299-1319.

VANDERVOLT, R. & BROOKS, S. M., 1977. Polyvinyl chloride film thermal decomposition products as an occupational illness. I. Environmental exposures and toxicology. *Journal of Occupational Medicine*, 19:188-191.

WALTER, I. D., 1972. Yellow fever vaccination, avian leukosis virus, and cancer risk in man. *Science*, 177:76-77.

VENA, J. E.; BYERS, T.; SWANSON, M. & COOKFAIR, D., 1982. Lung cancer in butchers? *Lancet*. 2:713.

WEISSENBURGER, D. D.; ARMITAGE, J. O. & PURTILO, D. T., 1986. Environmental Epidemiology of Non-Hodgkin's Lymphoma in Eastern Nebraska. *Federal Proceedings*, 46:640.

WILKLUND, K.; LINDEFORS, B. M. & HOLM, L.-E., 1988. Risk of malignant lymphoma in Swedish agricultural and forest workers. *British Journal of Industrial Medicine*, 45:19-24.

ZAHM, S. H. & WEISENBURGER, D. D., 1992. Sex difference in the risk of multiple myeloma associated with agriculture. *British Journal of Industrial Medicine*, 49:815-816.