TITLE PAGE

a) FINAL PROGRESS REPORT FOR GRANT

Title: “Cancer Risk in Workers Exposed to Oncogenic Viruses”
NIOSH/CDC 5 Ro1 OH008071-04
05/01/04-04/30/08
Principal Investigator: Eric S. Johnson, M.D., Ph.D., M.P.H., D.T.P.H.
Department of Epidemiology, School of Public Health,
UNT Health Science Center
3500 Camp Bowie Blvd.
Fort Worth
TX 76107
Phone: 817 735 0327
e-mail: ejohnson@hsc.unt.edu

Co-investigators:
Martha Felini, Ph.D. Project Coordinator, UNT Health Science Center

TABLE OF CONTENTS 2

LIST OF TERMS & ABBREVIATIONS

Cohort
Mortality
Cancer
Non-malignant Disease
Transmissible Agents
Oncogenic Viruses
Polycyclic Aromatic Hydrocarbons
Nitrosamines
Benzene
Phthalates
Fat/Cooking Aerosols
Smoke
Smokehouses
Wrapping Machine
Curing
Risk
Standardized Mortality Ratio
Proportional Mortality ratio
Odds Ratio
Follow-up
Tracing
Occupational
Poultry Slaughtering/Processing Plants
Workers
Exposure
Case-cohort
Chickens
Turkeys
Food Animals
Neurologic Diseases

ABSTRACT

Certain viruses naturally infect and cause cancer in chickens and turkeys. These include the retroviruses avian leucosis/sarcoma viruses (ALSV) and reticuloendothesiosis viruses (REV), and the herpesvirus Marek's disease virus (MDV). Infection is very common in birds destined for human consumption. Experimentally, cancer has been induced in primates infected with these viruses. These viruses have been shown to be capable of infecting human cells *in vitro*, and causing them to become cancerous. It has been shown that poultry workers and subjects in the general population are also commonly infected with these viruses. Human exposure to these viruses occur occupationally (workers in poultry slaughtering/processing plants and poultry farms, egg candlers, veterinarians, cooks, laboratory workers, etc.). The general population is also exposed through contact with live poultry, blood, secretions, raw meat, raw eggs and ingestion of raw or inadequately cooked poultry meat and eggs. Infection with ALSV also occurs through vaccination with live vaccines grown in chicken embryo cells such as measles, mumps and yellow fever vaccines. However, in spite of the scientific evidence accumulated thus far, definitive proof that can confirm beyond any doubt that these viruses cause cancer in humans is currently lacking. Two critical pieces of evidence are needed to incriminate these viruses as causing cancer in humans: 1) laboratory demonstration of ALSV integrated within the human genome, and 2) epidemiologic evidence of excess cancer occurrence in human exposed to these viruses.

We have therefore been studying mortality in workers in poultry slaughtering/processing plants. These workers have the highest human exposure to these viruses, since they come into contact with thousands of chickens and turkeys daily at work and handle the internal organs, blood and secretions, and they get cuts and bruises in their skin that facilitate entry of microorganisms into their body. We reason that if these viruses cause cancer in humans, then it should be readily evident in workers in poultry slaughtering/processing plants.

We therefore conducted two types of studies for the awarded grant:

1) A cohort mortality study of 20,131 workers in poultry slaughtering/processing and a comparison group of 10,356 control workers in the seafood industry. These workers were identified from rosters of various unions of the United Food & Commercial Workers Union (UFCW) International. The rosters were from the Baltimore Meatcutters' Union, the Missouri Poultry Union, and a multi-state Union Pension Fund. Follow-up of these three cohorts has been completed, and we are in the process of analyzing the data, and some results are available.

The results indicate that a total of 10 major cancer sites were observed to be occurring in excess in the cohort of poultry workers or in particular race/sex subgroup(s) of it. These are 1) cancers of the buccal & nasal cavities and pharynx; 2) esophagus; 3) rectum, recto-sigmoid junction, anus; 4) liver & intrahepatic bile ducts; 5) pancreas; 6) trachea, bronchus, and lung; 7) ovary; 8) brain; 9) tumors of the hemopoietic/lymphatic systems combined (including multiple myeloma, lymphoma, lymphoid leukemia, myeloid leukemia, monocytic leukemia, myelofibrosis); and 10) cancer of the gallbladder and extrahepatic ducts. These increased risks were not limited to cancers only but were also observed for neurologic diseases, cardiovascular diseases, and diseases of the urinary system. Two papers on cancer and noncancer mortality in the Baltimore cohort have been submitted for publication. We are preparing manuscripts for publication for the Missouri and Pension Fund cohorts separately and for all poultry cohorts combined.

2) A pilot case-cohort study of selected cancers within these three cohorts combined. The base population for the case-cohort study from which cases and controls were selected was defined as all subjects in the cohort study above, who were alive as of 01/01/1990 (N=43,904). The cases consist of the following cancer sites: cancers of the 1) lung, 2) buccal & nasal cavities &

pharynx, 3) esophagus, 4) rectum, recto-sigmoid junction & anus, 5) liver, 6) pancreas, 7) brain, 8) kidney, 9) bladder, and 10) tumors of the hemopoietic lymphatic systems. These cases were selected because they were identified in previous follow up of some of the studied cohorts to be occurring in excess in workers in poultry slaughtering/processing plants. As it turned out nearly all of these sites were also confirmed to be in excess in the study being reported on here. More detailed analyses are in progress, and to date we have results for cancers of the lung, pancreas, and liver.

Specific jobs or tasks within the poultry industry were observed to be associated with each of these three cancers, especially tasks associated with exposure to oncogenic viruses and other transmissible agents, such as exposure to live animals and slaughtering activities in which exposure is highest. Also, exposure to fumes from the wrapping machine that contain carcinogenic benzene, polycyclic aromatic hydrocarbons (PAH) and phthalates was identified as another risk factor associated with excess occurrence of these three cancer types. Similarly exposure to PAH during smoking of meat was associated with excess cancer risk. In addition, we were able to confirm established occupational risk factors outside the meat and poultry industries and non-occupational risk factors for these cancer types.

The findings of this study provide sufficient information that requires immediate steps to be taken to protect poultry workers during carrying out tasks that put them at risk of exposure to transmissible agents, which holds for virtually all workers, and to protect them from exposure to chemical carcinogens emitted during wrapping and smoking of meat. Protective measures may include engineering interventions, education, protective clothing and appropriate gloves, etc. Also, importantly the implication of these findings is that the general population may be at risk of developing cancer from exposure to live poultry or their products or from ingesting raw or inadequately cooked poultry products, or even from receiving vaccines contaminated with poultry oncogenic viruses such as ALSV. This may present a major public health problem and further studies are urgently needed to investigate this real possibility.

Uniquely for the first time ever, we investigated a total of 185 causes of death. This many causes of death has not been previously investigated in any occupational mortality study published previously.

HIGHLIGHTS AND SIGNIFICANT FINDINGS

The cohort mortality study found that workers in poultry slaughtering/processing plants have increased mortality from several cancer sites. These are 1) cancers of the buccal & nasal cavities and pharynx; 2) esophagus; 3) rectum, recto-sigmoid junction, anus; 4) liver & intrahepatic bile ducts; 5) pancreas; 6) trachea, bronchus, and lung; 7) ovary; 8) brain; 9) tumors of the hemopoietic/lymphatic systems combined (including multiple myeloma, lymphoma, lymphoid leukemia, myeloid leukemia, monocytic leukemia, myelofibrosis); and 10) cancer of the gallbladder and extrahepatic ducts. The findings were not limited to cancers only, but were also observed for neurologic diseases, cardiovascular diseases, and diseases of the urinary system. In many cases, the risks were extremely high suggesting that working in these plants was causally related to the excess occurrence of these diseases. Because this was a retrospective cohort morality study it was not possible to determine whether occupational exposures (if so, which) or non-occupational exposures were responsible for these occurrences.

However, we have thus far analyzed the pilot case-cohort data for three cancer sites that were in excess in the cohort mortality study, viz: lung, pancreas and liver, in which detailed information on occupational and non-occupational exposures were collected. The results indicate that occupational activities associated with the highest exposure to transmissible agents (especially oncogenic viruses) such as contact with live animals and blood, and slaughtering, were associated with very high risks of death from cancers of the lung, pancreas and liver, after controlling for tobacco smoking. The findings also confirmed previous findings of ours and others that occupational contact with live cattle, pigs and sheep in stockyards and slaughtering of these animals were associated with very high risks of lung cancer even after controlling for tobacco smoking.

Overall there was a slight to moderate increased risk of lung cancer associated with exposure to fumes while using the wrapping machine. However, the risk increased significantly when confined to women (this activity is predominantly carried out by women).

The study found that smoking of poultry was associated with high risk of liver cancer in poultry workers, after controlling for tobacco smoking.

Of the other potentially carcinogenic occupational exposures of interest that occur in poultry plants, there was no evidence that exposure to nitrosamines was associated with lung, pancreas or liver cancer.

The study confirmed known *established* risk factors for cancers of the lung, pancreas and liver, such as tobacco smoking, exposure to gasoline (for lung cancer), exposure to dyes, pancreatitis, and tobacco smoking (for pancreatic cancer), and exposure to hepatitis virus, cirrhosis, and surrogate for aflatoxin exposure (for liver cancer).

In addition, new associations detected were eating of salted meat and association with cancer of the pancreas, warts on the body (papilloma virus) for lung cancer, and infectious mononucleosis and liver cancer.

The study being reported on is unique in that we examined 185 specific causes of death. This is the first time ever that this many causes have been investigated in any occupational cohort mortality study anywhere in the world. Thus exciting new findings that have never been reported on before were observed.

TRANSLATION OF FINDINGS

1) Engineering and ventilation controls and best practices should be introduced to further minimize aerosol transmission of transmissible agents throughout the plant, and to minimize airborne exposure to aerosols fumes and smoke from the wrapping machine and during smoking and frying of poultry.

2) Use of the “hot wire” and “cool rod” wrapping machine should be terminated and these machines replaced with ones that do not involve thermal decomposition of the plastic film used to wrap meat, e.g., use of a mechanical blade to cut the film.

3) Educate workers, employers and unions on the potential hazards associated with various tasks and exposures within the industry and measures to be taken to protect workers.

4) Provide workers with appropriate protective equipment and body wear such as special gloves that will protect them against injury from knives, mechanical saws, and sharp bone splinters, to minimize entry of microorganisms into the body.

5) Efforts should be made to eradicate, control or reduce infectious agents in poultry birds and food animals in general, in farms prior to slaughter.

6) Use of closed oven systems for smoking and frying meat that does not involve worker exposure to smoke.

OUTCOMES/RELEVANCE/IMPACT

This study has identified several occupational exposures that present carcinogenic hazards to workers in poultry slaughtering/processing plants, and even poultry workers in general in some cases. Later reports will deal with potential occupationally-induced non-malignant diseases also. The findings of adverse outcomes (cancer & non-cancer) related to occupational exposure to transmissible agents in these workers have far reaching implications beyond the occupational setting since exposure to transmissible agents in food animals and animal food products is virtually universal in the general population, hence this study hypothesizes that some of the common diseases occurring in the general population (certain cancers, neurologic, cardiovascular and urinary diseases) may be due to exposure to transmissible agents present in live animals used for food or their raw products.

Epidemiologic and laboratory-based studies are urgently needed that will begin to attempt to identify which specific biological or chemical agent is the cause for each of the diseases excess risk was observed for.

There is need for research studies to better characterize the various exposures incriminated in the industry.

SCIENTIFIC REPORT

Background

Certain viruses either in their exogenous or endogenous form naturally and commonly infect and cause cancer in chickens and turkeys and other animals (Witter, 1991; Johnson, 1994a). The viruses include 1) the avian leukosis/sarcoma viruses (ALSV), reticuloendotheliosis viruses (REV) which are retroviruses, and Marek's disease virus (MDV), a herpesvirus (Payne 1985; Payne 1987; Witter, 1991). While some members of the ALSV and REV family of retroviruses usually induce a lymphoid leukosis-type tumor which takes months to develop and which is endemic in up to 5% of birds, occasionally epidemics occur, and tumor incidence is much higher. Moreover, other members of the family such as the acute transforming viruses that carry oncogenes are highly oncogenic and are among the most potent cancer-causing agents known to man, and can induce tumors in chickens or turkeys in a matter of days, with incidence of tumors approaching 100% in some cases (Witter, 1991; Johnson, 1994a). These viruses induce a wide variety of tumors in poultry birds which include several types of leukemias/lymphomas, soft tissue sarcomas, osteopetrosis, cancers of the lung, kidney, liver, pancreas etc. (Payne, 1987; Payne et al, 1992). However, whether they cause cancer in humans has not been established, although evidence is accumulating that suggests they may have an etiologic role in the occurrence of human cancers. We initially hypothesized that these agents may cause infection and similar cancers in humans. To investigate this we have been engaged in conducting cohort mortality studies of workers in poultry slaughtering/processing plants.

Human Exposue to ALSV, REV and MDV

Human exposure to these potent oncogenic viruses is widespread. The viruses are present in otherwise apparently healthy chickens and turkeys destined for human consumption, and their products such as eggs. Thus the viruses may be present in raw meat and raw eggs or inadequately cooked meat and eggs. Using a highly sensitive reverse-transcriptase assay, in a random survey by us of eggs displayed for sale in supermarkets in the New Orleans metropolitan area, the presence of ALSV was detected in at least 14% of the eggs (Pham et al, 1999a; Pham et al 1999b).

In addition, exogenous viruses of the ALSV group have been known to be present as contaminants in early preparations of vaccines grown in chicken embryo cells used during World War II (Waters et al, 1972). Measures were taken to eliminate the occurrence of these viruses in vaccines through the use of ALSV- and REV-free embryos for vaccine use. However, recently, reports have surfaced again on the presence of reverse transcriptase activity associated with viral particles in currently used measles, yellow fever, mumps and possibly influenza vaccines (WHO Weekly Epidemiologic Records, 1996; Boni et al 1996). The World Health Organization out of concern over these reports recently assembled a panel of experts to advise on the implications for health (WHO Consultation on Issues Related to the Presence of R-tase Activity in Chicken Cell Derived Vaccines, Geneva, April 24-25, 1998). New data presented at this meeting now confirm that the particle-associated reverse transcriptase activity detected in currently used vaccines is due to the presence of both endogenous ALSV and endogenous avian viruses (EAV) as contaminants in these vaccines. The panel recognized the dearth of epidemiologic studies on risk associated with exposure to ALSV, and recommended that epidemiological studies on the occurrence of cancer in ALSV-exposed populations be urgently undertaken (WHO Weekly Epidemiological Record, 1998; WHO Consultation on Issues Related to the Presence of R-tase Activity in Chicken Cell Derived Vaccines, Geneva, April 24-25, 1998). A recent study by the Centers of Disease Control report that virtually all stocks of measles and mumps vaccine currently in use in the United States are contaminated with the endogenous forms of ALSV (Tsang et al, 1999).

Exposure also occurs occupationally among subjects exposed to poultry such as poultry farmers, poultry breeders, laboratory workers, veterinarians, egg candlers, workers who handle raw chickens and turkeys such as cooks, workers in the meat department of supermarkets, and workers in poultry slaughtering/processing plants who have the highest exposure.

Thus human exposure to these viruses is virtually universal. The viruses can survive long enough in the external environment to cause infection. For example, 45% of commercial eggs stored in the refrigerator at 8°C for 0 to 6 days, and 21% for 7 to 34 days, still contained infectious lymphoid leukosis virus (Spencer et al, 1976). Marek's disease virus can survive at room temperatures of 22° to 25° C for up to 4 days, and up to two weeks at 4° C (Calnek & Adldinger, 1971).

Oncogenic potential for humans

1) Experimentally, ALSV and REV can infect and transform human cells *in vitro* (Stenkvist and Ponten, 1976; Koo et al, 1991; Johnson & Griswold,1997).

2) Experimentally, ALSV can infect and induce tumors in mammals, including primates, *in vivo* (see review by Johnson, 1994a).

3) Poultry workers as well as a high proportion of subjects in the general population with no known occupational exposure to poultry, have antibodies in their blood directed against ALSV, REV and MDV, indicating widespread exposure to these viruses (Johnson et al 1995a; Johnson et al, 1995b; Choudat et al, 1996).

4) The only two cohort mortality studies of workers in poultry slaughtering/processing plants conducted to date indicate excess occurrence of certain cancers (Johnson et al, 1986; Johnson et al 1997; Netto et al, 2003). A study of a third cohort did not report on specific cancers (Fritschi et al, 2003). Moreover an initial pilot study by us of tumors of the hemopoietic lymphatic systems nested within one of these cohorts also identified working in chicken slaughtering/processing plants as a risk factor for the occurrence of these tumors in the cohort (Metayer et al, 1998).

Prior to the study being reported on here, there have been only two cohort cancer mortality studies of workers exposed to poultry published to date in the literature. Both were conducted by us and the cohorts consisted of 2,580 workers in the Baltimore poultry cohort and 7,700 workers in the Missouri poultry cohort. These workers were identified from union rosters and were employed in plants where poultry birds were slaughtered and processed. Workers in poultry slaughtering/processing plants have the highest human exposure to transmissible agents that are present in poultry and their products such as raw or inadequately cooked poultry meat and eggs. Some of them are viruses that infect and cause cancer in chickens and turkeys, and are among the most potent cancer-causing agents known in animals. We reasoned that if these agents cause cancer in humans, it will be most readily evident in this highly exposed occupational group. Our previous studies of two of these cohorts indicated that indeed certain cancers were occurring in excess.

The present study was conducted to update mortality in these two cohorts and to study an additional cohort of 20,131 workers in poultry slaughtering/processing plants identified from a Pension Fund. The overall goal was to see if the initial findings could be replicated in this combined cohort of 30,411 poultry workers (the largest and only study to date of these workers), and to conduct a pilot case-cohort study nested within this combined cohort, of selected cancer sites observed to be occurring in excess in the previous two cohorts we had studied, in order to identify specific exposures responsible for the excess cancer occurrences.

Specific Aims

The main objective of this proposed study is to investigate cancer mortality in workers in poultry slaughtering/processing plants. This group of workers have the highest human exposure to the oncogenic viruses of poultry. Also, these workers belong typically to the lowest socioeconomic stratum and are among the lowest paid individuals in industry, with wages around the minimum allowed by law. In spite of the fact that they are exposed at work to viruses that are among the most potent cancer-causing agents known in animals, they have not been purposefully studied for cancer risk in analytic epidemiologic studies. Specifically, we aim to do the following:

1. To assemble and combine three main cohorts of over 30,000 subjects who worked in poultry slaughtering/processing plants where high exposure to poultry oncogenic viruses occurred, and who were members of any one of several unions which drew their membership from a geographically wide

area of the United States. Two of the three cohorts (Baltimore & Missouri unions) have been studied before, and their mortality will be updated. The third cohort (Chicago Pension Fund) had already been assembled, but not yet studied.

2. To study cancer mortality and mortality from other causes in subjects in this combined cohort over a 50-year period, i.e., from their date of union membership (date of hire) which goes back as early as 1949, to the end of 2003. Mortality in the combined cohort will be compared with that in the United States general population to determine whether this group of workers with this unique exposure has increased mortality from specific cancer types, and other causes of death.

3. While this proposed study (Phase 1) is in progress, to conduct in Phase 2 a case-cohort study of cancer sites observed to be occurring in workers in poultry slaughtering/processing plants in the two cohorts we had previously studied. This will permit a more definitive determination of the role of these viruses in the occurrence of any increased risks observed in Phase 1, as we will be able to obtain more detailed information on life-time occupational and non-occupational exposures related to poultry, as well as potential occupational and non-occupational confounding factors. We will also investigate the role of other potentially carcinogenic exposures within the industry in the occurrence of the excess of these cancers, viz: 1) fumes (containing carcinogenic polycyclic aromatic hydrocarbons (PAH), benzene, and phthalates), emitted from the wrapping machine used to wrap poultry; 2) exposure to smoke emitted from smokehouse where poultry birds are smoked; 3) exposure to nitrosamines during the curing of poultry products; exposure to heterocyclic amines and PAH emitted during the frying of poultry in some of these plants.

Procedures & Methodology

A. COHORT MORTALITY STUDY

A cohort mortality study of subjects who worked in poultry slaughtering & processing plants was conducted as follows:

1) Mortality was updated in a cohort of 2,580 poultry workers from 5 chicken slaughtering/processing plants for the period 1990-2003. These subjects belonged to the United Food and Commercial Workers (UFCW) Meatcutters' union in Baltimore, and their mortality had previously been studied for the period 1949-1989 during which time 380 deaths occurred (Johnson et al 1986a; Johnson et al 1986b; Johnson 1989; Johnson 1994b; Johnson et al 1995c; Johnson et al 1997). In addition, a control group of 6,052 subjects who worked in non-poultry and non-meat companies such as soft drinks manufacturing, oyster shocking, etc., and who were part of the Baltimore meatcutters' union were also studied for comparison.

2) Mortality was updated in another cohort of 7,700 poultry workers from 5 plants for the period 1991-2003. These subjects belonged to the UFCW poultry union in Missouri, and their mortality had previously been studied for the period 1969-1990 during which time 459 deaths occurred (Netto & Johnson, 2003).

3) Mortality was studied for the first time for the period 1975-2003 in a new cohort of 20,131 poultry workers from 11 poultry plants belonging to a UFCW Pension Fund. These workers were members of local poultry unions located in 6 states (Alaska, Arkansas, Louisiana, Maine, Missouri, Texas). A group of 10,356 subjects who were members of the same union Pension Fund between 1/1/1973 and 12/31/1989 but who worked in 21 seafood companies provided an occupational comparison group not exposed to poultry. These companies were located in 8 States, distributed as follows: Florida, Illinois, Indiana, Massachusetts, New Jersey, Ohio, Pennsylvania, and Texas. Mortality in this cohort was studied from 1/1/1973 to 12/31/2003 for these control workers.

Thus we studied a total of 30,411 subjects from 21 poultry plants exposed to the oncogenic viruses of poultry. Information present in union and Pension Fund records in this study includes name, date of birth, sex, social security number, address, name of next-of-kin, name of company, dates of monthly union dues payment, unique membership number, date of union application, date of death, and date of termination of dues payment. Membership in the unions involved is compulsory within 30 days of employment, thus dates of payment of *full* union dues correspond to dates of employment. Partial dues payment (an amount less than the full amount for that year, or absence of union dues payments, are indicative of periods of termination of employment (e.g. retirees, layoffs,etc).

1) Main Methods of Follow-up

1. National Death Index
2. The Pension Benefit Information Company

2) Secondary Methods of Follow-up

1. Personal Contact (telephone, mailing, post office, etc.)
2. Equifax Credit Bureau
3. State Departments of Vital Records
4. Internet Methods (Private Eye, Ancestry.com, Polk Directory)

The following strategy was used for follow-up:

1) Follow-up through the National Death Index (NDI)

A listing of all subjects not known to be actively paying dues and not known to be dead was sent to NDI for the identification of deceased subjects. The NDI search (NDI Plus) was carried out only for the update periods of follow-up for the Baltimore (1990-2003) and Missouri (1991-2003) cohorts, since these cohorts have previously been studied. For the Pension Fund cohort, the search was from 1979, the earliest date an NDI search is possible up to the end of 2003. Virtually all of the deaths occurring in subjects with full date of birth or social security number in the Baltimore, Missouri and Pension Fund cohorts during the period (1990-2003, 1991-2003 and 1979-2003, respectively) were identified using this method.

The NDI allows matching based on name, race, sex, marital status, State of residence, State of birth, social security number, date of birth and father's surname. When social security number is included in matching variables, NDI has been shown to correctly identify between 92% and 99% of deaths. When social security numbers were not used, between 80% and 96.5% of deaths are correctly identified (Patterson & Bilgrad, 1986; Schall et al, 2001). An NDI Plus search results in the identification of deceased subjects, as well as providing information on the causes of death.

2) Follow-up through the Pension Benefit Information Company (PBIC)

The same list sent to NDI was simultaneously sent to the PBIC. Located in California, this company matches subjects against US death records for all years from the 1800s to the present using information received from the Social Security Administration (SSA), Health Care Financing Administration (HCFA), Civil Service Commission, Railroad Retirement Board, Department of Defense, and the Departments of Vital Records of various States including all the States from which the study population is derived. Customers include Fortune 500 companies, Federal Agencies such as US Treasury, and researchers. Deaths are updated monthly. Information used for matching includes the first and last names, date of birth, social security number, gender, and last known zip code. Since matching was against all years since the 1800s, it thus covered the relevant study period of 1949-2003. The PBIC will also perform searches for subjects without social security number or date of birth and provided a list of possible matches for each such person taking into account the source of the data, and the name of the State of origin of the subject.

Identification of deaths by the company was initially rigorously tested by researchers at the University of Pittsburgh (Schall et al, 2001). They compared the ability to correctly identify deaths in a cohort of 42,023 workers between 1945 and 1992, by the PBIC, SSA, and HCFA. A total of 746 confirmed deaths were identified by all three methods. PBIC independently identified 736 (99%) of these deaths. Of the 10 deaths not identified by PBIC, one was identified exclusively by SSA and 9 by

HCFA alone. It is not clear why PBIC missed the one death identified by SSA since PBIC searches included a SSA search. At the time of the Pittsburgh evaluation of PBIC tracing, the only State Department of Vital Records search included in the PBIC search was for the State of California, and a HCFA search was not included then. Since then, PBIC searches now include a search for deaths in the Vital Records Departments of all 11 States included in the present study, as well as a HCFA search. Thus PBIC appears capable of identifying virtually all the deaths that will occur in this study, especially during the pre-NDI period (prior to 1979), as long as matching information on date of birth and social security number is available.

It is to be noted that tracing by the SSA alone can identify deaths occurring as far back as 1937 to the present, and it has been shown for the period 1974-1980 for example, that with the availability of the full required matching information (last name and social security number), 87.8% of deaths can be detected (Wentworth et al, 1983). We ourselves have tested the sensitivity of this method. Out of 409 known deaths with Social Security number occurring between 1951 and 1979 that were matched to the SSA file, 388 (94.4%) were correctly identified (Johnson ES - Doctoral Thesis, Department of Epidemiology, Johns Hopkins School of Hygiene & Public Health, 1984).

It should be noted that the degree of success achieved in detecting deaths by the NDI and PBIC methods of follow-up depend on the accuracy of the social security number and date of birth information. While this information in union records matched perfectly that in the NDI and PBIC databases for the overwhelming proportion of subjects in the study, there were instances of possible matches in which the match was off by a single digit in the social security number or by a single day in the date of birth. In these situations we retrieved possible death certificates for the case, and attempted to make a definite match by further consideration of other potentially matchable data such as address or name of spouse or occupation contained in union records, or by use of other follow-up methods such as personal contact.

3) Follow-up of subjects with missing date of birth and social security number

In the Baltimore poultry cohort, 197 out of 2,580 poultry subjects (7.6%), had no date of birth and social security number. In the Missouri cohort, 344 out of 7,700 (4.5%) had no date of birth and social security number. In the Pension Fund cohort, only 128 of 20,341 individuals (i.e. 0.6%) had no social security number, and 1,465 (7.3%) had no date of birth. The missing information in the Pension Fund cohort was almost exclusively due to difficulty in reading the information from poorly prepared microfilms for a few particular plants. For these subjects additional follow-up methods apart from NDI and PBI were employed for identifying deaths in the group. For this small group of subjects, we relied on Credit Bureaus such as Equifax, and personal tracing by our own research staff using telephone numbers and addresses in special telephone directories such as Polk and Pro-Phone Disc., Internet methods, State Department of Vital Records, etc., to determine vital status.

3) Handling of lost subjects in the analysis

The majority of subjects with incomplete date of birth or no Social Security number tended to be people who worked for very short periods of time; e.g. in the Baltimore poultry cohort, 63% of the subjects without both date of birth and Social Security number worked for less than 12 months. Thus if necessary, additional analyses can be done in which subjects with less than 12 months of employment are excluded, which will further improve follow-up success rate, and comparison will made to see to what extent the results differ from those obtained when they are included in the analysis.

Also, we have previously shown that since individual methods of follow-up preferentially identify either dead or live subjects, e.g. State Departments of Vital Records identify only dead subjects, and follow-up by State Motor Vehicle Department preferentially identifies subjects who are alive, the usual practice of withdrawing subjects at the time of loss in the analysis, under the assumption that their subsequent mortality experience *as determined by use of these same methods* is the same as that of comparable subjects at the time of their loss who were successfully traced, may not be the most appropriate way of handling lost subjects, and in fact this procedure in certain circumstances may be associated with significant bias when there is an appreciable proportion of persons lost to follow-up (Johnson, 1990). It has been our practice to carry out two separate analyses, one in which lost subjects are withdrawn at the time of loss, and the other in which lost subjects are assumed to be alive at the end of the study, and this will be done during ongoing statistical analysis of the data. A close agreement between the two results is an excellent indication of how successful death ascertainment has been.

4) Coding of Death Certificates

In our previous follow-up studies, since we used the Monson program, all of the death certificates retrieved had been coded to the 8th ICD Revision irrespective of the ICD Revision in operation at the time of death, since the Monson program used US reference mortality rates which had been similarly coded to the 8th Revision, irrespective of date of death. For this study, we used the OCMAP Plus program from the University of Pittsburgh. This time all causes of death were coded to the 9th ICD Revision irrespective of the ICD Revision in use at the time of death, and we purchased US mortality rates coded to the 9th Revision also from the University of Pittsburgh.

5) Statistical Analyses for Cohort Mortality Study

We will conduct the following analyses:

1) Proportional Mortality Ratio (PMR) analyses
2) Standardized Mortality Ratio (SMR) analyses
3) Mortality odds ratios (for selected sites)
4) Poisson Regression

In the PMR and SMR analyses cohorts are being individually compared to the United States general population using the OCMAP Plus software with all deaths coded to the 9th ICD Revision. These analyses simultaneously control for race, sex, age, and calendar time. Features in OCMAP Plus include analysis of risk by age and calendar year of death, age and calendar year of first exposure, by duration of employment (exposure) and by time since first exposure (latency), etc. These analyses are done automatically by the program when the appropriate option is selected, and they are being included in the analysis of this study.

In the SMR analyses, for subjects who were already working in a plant before the start of follow-up for that plant or before the plant was unionized, their person-years will be accumulated as from the date of start of follow-up or the date of union membership, respectively. Such employees will also be analyzed separately as a potential survivor population. The earliest date of union membership in the cohort is July 1 1949. For subjects who joined the union at the time of first employment, person-years will be accumulated from their date of union membership. (Note: it is compulsory for all subjects in the study to become members of the union within one month of the start of employment - thus date of union membership is virtually the same as date of first employment). Each cohort will be stratified into four subgroups by race and sex (black males, black females, white males, white females), and each of these groups stratified according to age (5-year intervals) and calendar year at entry into the cohort (5-year intervals). Person-years contributed will be determined, and the corresponding calendar year race-sex-age-specific US rates will be applied to calculate the expected deaths (see below). Observed deaths are likewise distributed according to the various strata described for expected deaths. Observed and expected deaths for each cell are summed over all ages, and calendar years, and over all strata, and the SMR estimated as the total observed divided by the total expected.

Separate SMR analyses are conducted for each plant and for each of the three cohorts, and final SMRs are determined for all cohorts combined as a group by dividing the sum of the observed deaths over all plants, by the sum of the expected. Because of the exhaustive methods that will be employed to determine vital status, it is likely that close to all deaths will be ascertained. Thus in this study, subjects lost to follow-up will be considered alive at the end of the study. This approach gives a conservative estimate of the SMR, indicating the minimum risk. We will also carry out the alternative analysis in which for those lost to follow-up, person-years are counted only up to the time of loss.

Expected deaths for the PMR analysis are similarly calculated, adjusting for race, sex, age and calendar year, except that the proportion of all deaths due to the specific cause for that cell in the US population will be multiplied by the corresponding total number of deaths in the study population, to get the deaths expected for that cause.

We plan to conduct a limited mortality odds ratio (MOR) analysis (Miettinen & Wang, 1981) for specific subtypes of tumors of the hemopoietic/lympahatic systems such as multiple myeloma, to supplement the SMR analyses. In these analyses, all exposed deceased cases and non-cases in poultry workers we will be compared with all unexposed deceased cases and non-cases in the US general population. We will also repeat the same analyses but using a different definition of non-cases which would comprise of only deaths not observed to be occurring in excess in the SMR and PMR analyses (i.e. not associated with exposure). These analyses will be standardized for age, race, and gender (Miettinen & Wang 1981). Similarly we will conduct Poisson regression analyses, this time using the control group of non-poultry and non-meat workers as the comparison group. These analyses will control for age, race, gender, calendar period, and plant.

6) Results & Discussion of the Cohort Mortality Study

Statistical analyses are in progress. We have completed the main SMR and PMR analyses for the Baltimore cohort and have submitted two manuscripts for publication, one on the findings for cancers and the other for non-cancers. The results are summarized in Tables 1-3 below. This is the first time mortality in workers in poultry slaughtering and processing plants or in any occupational group, has been studied in such detail (185 specific causes of death). Poultry plant workers have one of the highest human exposures to a wide variety of *transmissible agents* present in poultry birds (viruses, bacteria, fungi, protozoa, helminths), and virtually all of them are exposed to a significant degree. In a typical large poultry plant as many as 175,000 chickens are killed daily. The workers are prone to cuts and other types of injury from sharp knives, bone splinters, etc., and to dermatitis from irritant enzymes and other body fluids from the birds, making it easy for microorganisms to enter the body via the skin. They also have intimate contact with the blood and internal organs of the birds, and they are also exposed to microorganisms through the airborne route.

In addition to transmissible agents other potentially carcinogenic exposures include 1) exposure to *fumes emitted from the 'hot wire' wrapping machine* which contains benzene, polycyclic aromatic hydrocarbons and phthalates. 2) exposure to smoke and aerosols containing potentially harmful agents such as polycyclic aromatic hydrocarbons and heterocyclic amines during the smoking and frying of chickens and turkeys. 3) Exposure to nitrosamines during the curing of poultry. These are the only other exposures of importance that are candidates to explain some of the excess risks observed in these workers. However, although it is known that at least one of the six plants in this study handled turkeys, it is not known whether smoking and frying were done in this or any of the other plants, neither is it known which plants used the 'hot wire' wrapping machine.

Malignant Diseases

In Table 1, results are for causes of death for which more than one death occurred in the poultry cohort and for which a statistically significant SMR or PMR was observed in any race/sex subgroup or in the total poultry cohort. These sites were cancers of the base of tongue, palate and other unspecified mouth, tonsil/oropharynx, nasal cavity/mid ear /accessory sinuses, esophagus, recto-sigmoid, liver/intrabiliary, malignant immunoproliferative disease/myeloma/plasma cell, lymphoid leukemia and myelofibrosis. As seen in Table 1, the SMRs for all of these sites were elevated in both men and women except those for tongue, tonsil & oropharynx, esophagus, and recto-sigmoid, which were elevated in men only and lymphoid leukemia in women only. Although cause-specific SMRs in the poultry group cannot be compared with those in the control group because their age distributions are significantly different, it is noteworthy that except for cancer of the recto-sigmoid colon/rectum/anus in nonwhite men *the SMRs for none of these sites was statistically significantly elevated in the control group of non-poultry workers*, even though this group was significantly older than the poultry group and experienced about three times as many deaths overall than the poultry cohort. The PMR results are not shown, but all SMRs reported as statistically significant in the poultry group were also statistically significant in the PMR analysis.

The results for poultry workers indicate statistically significant increased occurrence of deaths overall in white men and women, but not in their non-white counterparts. The reason for this is not known, but one can speculate that the differences could reflect a much more overall unfavorable mortality in the nonwhite general population compared to the white general population, that makes it more difficult to detect occupationally-induced mortality in non-whites, rather than occupational differences. Deaths from cancers overall were not significantly elevated in any particular subgroup. However, significantly elevated SMRs or PMRs for certain sites were observed.

It appears that cancers of the buccal cavity & pharynx are occurring in excess generally in the poultry cohort and affecting multiple sites in this anatomical area. A total of 10 deaths from this cause was observed in the poultry cohort and 10 deaths also were recorded for the much larger and older control group. Small numbers of deaths and inability to control for possible confounding factors such as tobacco smoke and alcohol ingestion limit interpretation of the findings, but possible occupational factors that could be responsible for the excess include oncogenic retroviruses which induce a multiple of tumor types in chickens,[1] and papilloma viruses. The prevalence of warts is known to be high in poultry workers and is known to be associated with the human papilloma virus type 7 which is uncommon in the general population. [10] Furthermore, it is now generally believed that at least certain types of oral cancer are caused by human papilloma viruses especially type 16.[11]

There appears to be a definite excess of cancer of the esophagus in men, but again, inability to control for confounding factors such as tobacco smoking and alcohol ingestion limits interpretation of the significance of this finding.

The excess of cancer of the rectum confined to non-white males only may be fortuitous as a significant excess of this cancer was also observed in the control group. Furthermore, these were exactly the same findings in the previous follow-up of both the poultry cohort and control group, and no additional deaths from this site have occurred in the poultry cohort since the last follow-up.

The excess of liver cancer and multiple myeloma seems confined to white men and white women only, and the reason for this is not known. The numbers involved are too small at this time to determine if these differences are real. Similarly, small numbers inhibit interpretation of the excess of lymphoid leukemia observed in non-white women only. While very high SMRs for myelofibrosis were observed in white male and non-white female poultry workers small numbers and the occurrence of elevated SMRs confined to the same race/sex groups in control workers precludes firm conclusions at the moment, and in fact may indicate that the excess is not real.

Exposure to transmissible agents present in poultry, and to fumes emitted during the wrapping, smoking or frying of poultry are prime candidates that may be responsible for some of the excess cancers observed in poultry workers. Some of the transmissible agents like avian leukosis/sarcoma viruses and reticuloendotheliosis viruses that infect and cause cancer commonly in poultry[1] are known to infect/transform human cells also *in vitro*[12-14] and to cause tumors in primates.[15] More importantly, it has been shown that poultry workers and subjects in the general population are infected with these viruses and have antibodies in their blood against them.[16-18] As mentioned above, human papilloma viruses are also candidates for explaining the excess of some of these cancers.[10] It is worthwhile to note that exceedingly high risk of death from zoonotic bacterial diseases and helminthiasis (up to 100-fold) is being observed in this poultry cohort (manuscript in preparation), thus confirming the possible role transmissible agents in the occurrence of the excess of some of these cancers. However, a cohort mortality of this type does not control for non-occupational confounding factors and is not suitable for identifying the specific occupational exposures responsible. This type of investigation is better handled using a nested case-control design. Also, many comparisons were made and the numbers involved in many cases were small, thus interpretation should be tempered with caution.

The statistically significant three- to four-fold increased risk of lung cancer seen in the first follow-up of this cohort in white females,[4] seems to be decreasing with time, (SMR = 1.8) at the second follow-up, and in this update (SMR =1.6 , 95% CI 0.8-2.8). This progressive decrease in risk could indicate that the initial findings were due to chance. On the other hand exposure to fumes from the wrapping machine, a possible occupational cause, [5,19-21] was significantly reduced after 1975, and could well explain these findings if the initial results were due to these fumes. Unfortunately not all poultry plants would have used the 'hot wire' wrapping machine which were known to give off fumes and to cause meat wrappers' asthma and chronic bronchitis, and it is not known which ones did in this study. In a follow-up of women who were exposed to fumes in the meat department of supermarkets we were able to clearly show that lung cancer risk decreased progressively after 1975 when the 'hot wire' wrapping machine was replaced with the 'cold rod' wrapping machine[22] - in that study, for subjects dying in 1970-1974 (SMR = 6.7 (95% CI 2.5-13.1); for those dying in 1975-1979 (SMR = 0.9 (95% CI 0.1-3.3); for those dying in 1980-1984 (SMR = 0.8 (95% CI 0.2-2.3); and for those dying in 1985-1989 (SMR = 1.7 (95% CI 0.8-3.1). Hence a similar phenomenon may be occurring in the poultry industry also. The study by Fritschi et al. also reported an elevated odds ratio of 1.5 for lung cancer for meat workers exposed to these fumes, which was not statistically significant. [7]

To our knowledge, there are no data on exposure patterns in poultry slaughtering & processing plants, especially along gender lines. Site visits at a couple of plants and enquiries from workers indicate that while there may be some division along gender lines in tasks performed, from time-to-time workers may get drawn into particular tasks based on demand for that activity irrespective of gender. For example, it is more likely that unloading of birds from trucks and killing of birds are primarily male jobs, while proportionately more women will be engaged in wrapping and packing. It is likely that exposure to transmissible agents is higher in men than in women because of these differences, particularly as men are exposed to live birds and are involved in slaughtering and in the early stages of processing before environmental factors such as exposure to heat, light, and dryness, significantly affect survival of microbial agents initially present in the animals and their products as they get exposed to the external environment. Thus it is possible that the gender differences seen in Table 1 reflect differences in the degree of exposure to transmissible agents between men and women, and in wrapping and other activities. Also, it should be noted that deaths overall were fewer in females, and this could also partly explain gender differences in risk. On the other hand, the following should be noted; 1) all lost subjects were assumed to be alive, hence the SMRs are deliberately underestimated; 2) the SMR results agreed very closely with the PMR results; 3) similar findings were also observed in another independent cohort of poultry slaughtering & processing plants workers from another union in Missouri.[6] Unfortunately the study by Fritschi et al. did not have sufficient statistical power to report on specific sites other than lung cancer. [7] It should be noted that unlike the situation for transmissible agents in which virtually all the poultry workers were probably exposed to these agents, characteristically in plants where frying or smoking of poultry is carried out, only small groups of workers are typically expected to be engaged in these activities, hence likely to have been exposed to each of these other candidate exposures. Hence it will take exceedingly high risks to detect any increased risk due to these other exposures.

We carried out analysis of risk by 'latency' – Table 2. All of the deaths for all of these sites occurred after 10 years from the time of first exposure except one death due to cancer of the esophagus. Caution should be exercised in interpreting latency analysis in mortality studies since the interval from time of first exposure to death includes also duration of illness, which for diseases of long duration may not be a good surrogate for true latency which is the interval from time of first exposure to onset of disease. The numbers involved at this time are too small for meaningful interpretation except to note that for some of these sites extremely high SMRs were observed for 10 or more years after onset of exposure.

At the moment the cohort is relatively young with only 31% deceased. It is possible that with longer accrual of latency more causes may be observed to be occurring in excess. Further follow-up to a point when the majority of the cohort will have died will provide more definitive results. However, at this time, the study provides enough evidence to recommend that this occupational group warrants detailed investigation, and consideration should be given to the possible need to protect workers against candidate exposures that may be responsible for the excess occurrences of some of these cancers. The group needs to be studied not only because of occupational reasons, but also because it is possible that transmissible agents present in poultry and poultry products could be transmitted to subjects in the general population,[23] from handling and ingestion of raw or inadequately cooked poultry products, or from exposure to live birds.

Table 1. Baltimore Poultry Workers - Standardized Mortality Ratios for the period 1954 to 2003 **(Malignant Diseases)**

Cause of death	Poultry Workers						Control Group					
	Non-white Males	White Males	All Males	Non-white Females	White Females	All Females	Non-white Males	White Males	All Males	Non-white Females	White Females	All Females
	Obs. SMR (Conf. Int.)	Obs. SMR (Conf. Int.)	Obs. SMR (Conf. Int.)	Obs. SMR (Conf. Int.)	Obs. SMR (Conf. Int.)	Obs. SMR (Conf. Int.)	Obs. SMR (Conf. Int.)	Obs. SMR (Conf. Int.)	Obs. SMR (Conf. Int.)	Obs. SMR (Conf. Int.)	Obs. SMR (Conf. Int.)	Obs. SMR (Conf. Int.)
Death from all malignant neoplasms	77 1.0 (0.8–1.2)	22 0.9$ (0.6 – 1.4)	99 1.0 (0.8 – 1.2)	49 1.0 (0.7 – 1.3)	39 1.3 (0.9 – 1.8)	88 1.1 (0.9 – 1.3)	161% 0.8 (0.7-1.0)	171 1.1 (0.9-1.3)	332 1.0 (0.9-1.1)	136 0.9 (0.8-1.1)	93** 0.8 (0.5-0.9)	229$$ 0.8 (0.7-1.0)
Base of Tongue	2 3.0 (0.4-11.0)	1 7.2 (0.2-40.2)	3 3.8# (0.8 – 11.0)	0 - -	0 - -	0 - -	2 1.4 (0.2-5.0)	0 - -	2 0.9 (0.1-3.1)	0 - -	0 - -	0 - -
Palate/other unspec. mouth	1 2.7 (0.1-14.9)	0 - -	1 2.2 (0.1-12.3)	1 9.6# (0.2-53.3)	0 - -	1 6.4 (0.2-35.9)	1 1.2 (0.0-6.7)	0 - -	1 0.8 (0.0-4.2)	1 3.1 (0.1-17.4)	0 - -	1 1.7 (0.0-9.4)
Tonsil; oropharynx	3 5.3* (1.1-15.6)	0 - -	3 4.6# (1.0-13.5)	0 - -	0 - -	0 - -	3 2.5 (0.5-7.4)	2 3.9 (0.5-14.0)	5 2.9 (1.0-6.9)	0 - -	0 - -	0 - -
Nasal cavity/ mid ear, acc sinus @	1 7.7# (0.2-43.0)	0 - -	1 6.2# (0.2–34.4)	0 - -	1 38.9# (1.0–217)	1 14.5# (0.4 – 80.9)	0 - -	1 5.0 (0.1-27.6)	1 2.0 (0.1-11.2)	0 - -	0 - -	0 - -
Esophagus	6 1.4 (0.5 – 3.1)	4 5.6* (1.5–14.5)	10 2.1# (1.0 – 3.8)	0 - -	0 - -	0 - -	7 0.7 (0.3-1.5)	4 0.9 (0.2-2.3)	11 0.8 (o.4-1.4)	3 0.9 (0.2-2.7)	1 0.8 (0.0-4.5)	4 0.9 (0.2-2.3)
Recto-sigmoid, rectum, anus	4 3.2# (0.9–8.2)	0 - -	4 2.3 (0.6 – 5.9)	0 - -	0 - -	0 - -	7 2.3 (0.9-4.8)	5 1.6 (0.5-3.8)	12* 2.0 (1.0-3.4)	1 0.4 (0.0-2.2)	2 0.9 (0.1-3.2)	3 0.6 (0.1-1.8)
Liver, intrabiliary	1 0.4 (0.0-2.0)	1 2.1 (0.1-11.7)	2 0.6 (0.1-2.2)	0 - -	2 5.4# (0.6-19.4)	2 1.5 (0.2-5.5)	5 0.8 (0.3-1.9)	3 1.0 (0.2-2.9)	8 0.9 (0.4-1.7)	4 1.5 (0.4-3.8)	0 - -	4 0.9 (0.2-2.3)
Malig. Immun, myeloma, plasma cell	1 0.6 (0.0-3.3)	2 5.3# (0.6-19.1)	3 1.5 (0.3-4.2)	0 - -	1 2.2 (0.1-12.5)	1 0.6 (0.0-3.2)	1 0.2 (0.0-1.3)	1 0.4 (0.0-2.2)	2 0.3 (0.0-1.1)	2 0.5 (0.1-1.8)	2 0.9 (0.1-3.4)	4 0.6 (0.2-1.6)
Lymphoid leukemia	0 - -	0 - -	0 - -	2 5.9# (0.7-21.5)	0 - -	2 3.5 (0.4-12.6)	0 - -	2 0.9 (0.1-3.4)	2 0.5 (0.1-1.9)	1 0.8 (0.0-4.4)	0 - -	1 0.4 (0.0-2.1)
Myelofibrosis@	0 - -	1 13.8# (0.3-76.9)	1 4.8 (0.1 – 26.8)	1 11.6# (0.3-64.8)	0 - -	1 6.5 (0.2 -36.4)	0 - -	2 4.0# (0.5-14.4)	2 2.3 (0.3-8.5)	1 3.4 (0.1-18.8)	0 - -	1 1.5 (0.0-8.4)
All lymp. & hemop. systems	4 0.7 (0.2-1.7)	2 0.8 (0.1-2.9)	6 0.7 (0.3-1.5)	3 0.8 (0.2-2.3)	1 0.4 (0.0-2.1)	4 0.6 (0.2-1.6)	4** 0.3 (0.0-0.9)	12 0.7 (0.4-1.3)	16$$ 0.5 (0.3-1.0)	6 0.5 (0.2-1.2)	2$$ 0.2 (0.0-0.8)	8$$ 0.4 (0.1-0.8)
All deaths	340 1.0 (0.9 – 1.1)	132 1.3** (1.0 – 1.6)	472 1.0 (0.9 – 1.1)	198 1.0 (0.9 – 1.2)	120 1.4** (1.1 – 1.7)	318 1.1* (1.0 – 1.3)	641** 0.8 (0.7-0.9)	744** 1.2 (1.1-1.3)	1385 1.0 (0.9-1.0)	477$$ 0.8 (0.7-0.9)	426 0.9 (0.8-1.0)	903$$ 0.8 (0.8-0.9)

$ PMR statistically significantly decreased (not shown)
# PMR statistically significantly increased (not shown)
% Statistically significantly decreased at the 95% confidence level
* Statistically significantly increased at the 95% confidence level
** Statistically significant ly increased at the 99% confidence level
@ The combined male & female PMR
Benign neopl. of lip/oral cavity/pharynx oth dig SMR for NWM = 45.8* (1.1-255), N=1 Total N=1

Table 2. Summary of Latency Results for **Malignant Diseases -** Baltimore Poultry (1954-2003)

Cause of Death	**Latency 0-9 Years**		**Latency 10-19 Years**		**Latency 20-29 Years**		**Latency 30 or more Yrs**	
	Males **Obs** **SMR** **95% CI**	**Females** **Obs** **SMR** **95% CI**	**Males** **Obs** **SMR** **95% CI**	**Females** **Obs** **SMR** **95% CI**	**Males** **Obs** **SMR** **95% CI**	**Females** **Obs** **SMR** **95% CI**	**Males** **Obs** **SMR** **95% CI**	**Females** **Obs** **SMR** **95% CI**
All Malignant Diseases	5 0.5 (0.2-1.3)	5 0.8 (0.2-1.8)	22 1.2 (0.8–1.8)	18 1.3 (0.8–2.1)	37 1.2 (0.8-1.6)	32 1.3 (0.9-1.8)	35 0.8 (0.6-1.1)	33 0.9 (0.6-1.3)
Disease of the Tongue	-	-	3 17.1 (3.5–50.1)	-	-	-	-	-
Palate/Other Unspecified mouth	-	-	-	1 32.0 (0.8-178)	-	-	1 6.6 (0.2-36.7)	-
Tonsil & Oropharynx	-	-	-	-	1 4.5 (0.1-25.0)	-	2 8.4 (1.0-30.2)	-
Nasal cavity Mid ear, Acc Sinus	-	-	-	-	-	1 47.8 (1.2-266)	1 19.6 (0.5-109)	-
Esophagus	1 2.2 (0.1-12.0)	-	3 3.2 (0.7-9.4)	-	4 2.6 (0.7-6.6)	-	2 1.0 (0.1-3.8)	-
Recto-sigmoid, Rectum, Anus	-	-	2 6.0 (0.7-21.7)	-	1 2.0 (0.1-11.1)	-	1 1.4 (0.0-7.9)	-
Liver, intrabiliary	-	-	-	1 6.8 (0.2-38.0)	1 1.0 (0.0-5.4)	1 2.6 (0.1-14.5)	1 0.6 (0.0-3.5)	-
Malignant Immun., Myeloma, Plasma Cell	-	-	1 3.2 (0.1-18.1)	-	1 1.6 (0.0-8.9)	1 1.9 (0.0-10.5)	1 1.0 (0.0-5.6)	-
Lymphoid leukemia	-	-	-	-	-	-	-	2 8.8 (1.1-31.7)
Myelobfibrosis	-	-	-	1 49.7 (1.2-276)	1 15.5 (0.4-86.6)	-	-	-
All lymphopoietic /hemopoietic Systems	1 0.9 (0.0-5.3)	1 1.7 (0.0-9.2)	1 0.6 (0.0-3.5)	-	3 1.2 (0.3-3.6)	1 0.5 (0.0-3.0)	1 0.3 (0.0-1.6)	2 0.7 (0.1-2.5)

Table 3. Baltimore Poultry Workers - Standardized Mortality Ratios for the period 1954 to 2003 **(Non-malignant Diseases)**

Cause of Death	Non-White Males	White Males	Total Males	Non-White Females	White Females	Total Females	Total Males & Females
	N0. Obs. SMR (95% CI)	No. Obs. SMR (95% CI)	No. Obs. SMR (95% CI)	No. Obs. SMR (95% CI)	No. Obs. SMR (95% CI)	No. Obs. SMR (95% CI)	No. Obs. SMR (95% CI)
Certain zoonotic bacterial diseases		1 295** (1.5-2192)	1 52.9* (1.3-295)	1 106* (2.7-592)		1 78.8* (2.0-439)	2 63.3** (3.3-294)
Helminthiasis				2 468# (279-787)		2 319# (177-576)	2 124# (55.8-275)
Disorders of @ thyroid gland	1 12.0# (0.3-66.8)		1 9.7# (0.2-54.2)	1 5.5# (0.1-30.8)		1 4.1 (0.1-22.9)	2 5.8# (0.7-20.9)
Diabetes	6 0.7 (0.2-1.5)	5 2.6 (0.8-6.0)	11 1.0 (0.5 – 1.8)	10 1.1 (0.5-2.0)	11 4.3** (1.7-9.0)	21 1.8* (1.1 – 2.7)	32 1.4 (1.0-2.0)
Senile & presenile psychotic conditions				3 3.3# (0.7-9.8)		3 2.0 (0.4 – 5.8)	3 1.1 (0.2-3.3)
Anterior horn disease	2 6.0# (0.7-21.7)	1 4.6 (0.1-25.5)	3 5.4* (1.1 – 15.9)		1 3.7 (0.1-20.7)	1 2.1 (0.1 – 11.6)	4 3.9* (1.1-9.9)
Myasthenia Gravis	1 20.4# (0.5-114)	1 44.6* (1.1-248)	2 28.0** (1.4 – 130)				2 14.6* (1.8-52.6)
Hypertensive disease	8 0.8 (0.7-1.2)	6 5.9** (1.5-15.4)	14 1.3 (0.7 – 2.2)	7 1.0 (0.4-2.0)		7 0.8 (0.3 – 1.7)	21 1.1 (0.7-1.7)
Ischemic Heart disease	56 1.0 (0.7-1.2)	31 1.2 (0.8-1.7)	87 1.0 (0.8-1.3)	33 1.0 (0.7-1.4)	27 1.8** (1.0-292)	60 1.2 (0.9-1.6)	147 1.1 (0.9-1.3)
Intracerebral hemorrhage etc	**		**	4 0.9 (0.3-2.4)	1 0.8 (0.0-4.6)	5 0.9 (0.3 – 2.1)	5 0.4* (0.1-0.9)
Diseases of @ Esophagus	1 4.6# (0.1-25.6)		1 3.5 (0.1 – 19.3)		1 18.6# (0.5-104)	1 6.7# (0.2 – 37.5)	2 4.6# (0.6-16.5)
Peritonitis				1 4.8 (0.1-26.5)	1 14.4# (0.4-80.1)	2 7.2# (0.9 – 25.8)	2 3.2 (0.4-11.6)
Other diseases of kidney & ureter				1 1.3 (0.0-7.5)	2 18.3* (2.2-66.0)	3 3.5# (0.7 – 10.3)	3 1.5 (0.3-4.4)
Transport accidents	16 1.2 (0.7-2.0)	11 2.8** (1.1-5.8)	27 1.6* (1.1 – 2.3)	3 1.1 (0.2-3.1)	2 1.1 (0.1-3.9)	5 1.1 (0.3 – 2.5)	32 1.5* (1.0-2.1)
Other Accidents	2 0.3 (0.0-1.0)	1 0.6 (0.0-3.6)	3 0.4# (0.1-1.0)	0	2 4.0 (0.5-14.4)	2 1.1 (0.1-4.0)	5 0.5 (0.2-1.1)
All causes of death	340 1.0 (0.9-1.1)	132 1.3** (1.0-1.6)	472 1.0 (0.9-1.1)	198 1.0 (0.9-1.2)	120 1.4** (1.1-1.7)	318 1.1 (1.0-1.2)	790 1.1 (1.0-1.1)

* Statistically significant at the 95% confidence level
** Statistically significant at the 99% confidence level
# PMR statistically significant (not shown)
Diabetes in Whites (N= 16, SMR = 3.6**, 95%CI = 1.9, 8.0)
Ischemic heart disease in Whites (N=58, SMR = 1.4*, 95%CI = 1.1, 1.8)
There were no deaths from Slow Virus infection of the CNS
Schizophrenia in (WF, N=1, SMR=71.4*); (entire poultry cohort, N=1, SMR=10.3)
Other Diseases of the Spinal Cord in (NWF, N=1, SMR = 25.2; for entire poultry cohort (N=1, SMR=6.8)
Malignant disease of the thymus/heart/mediastinum/pleura in (WF, N = 1, SMR=13.4**; for entire poultry group, N=1, SMR = 1.0)

Non-Malignant Diseases

The excess of diabetes observed in the previous update is also seen in the present follow-up. It is not clear why it seems restricted to whites only. We also observed an excess of diabetes in men who worked in the meat departments of supermarkets from this same union (14). It could be related to non-occupational factors such as obesity, or it could reflect an increased susceptibility to infection, since it is well known that diabetes is a strong predictor of infection-related mortality (15), or it could be due to a zoonotic transmissible agent(s), since an infective origin of the disease has been postulated (16).

The findings of increased mortality from neurological diseases like senile and pre-senile psychotic conditions, myasthenia gravis and anterior horn cell disease are novel and particularly very exciting, especially as (although based on small numbers), the increased risks appear very high, suggesting a causal association. The cause of myasthenia gravis in humans is not known, but it is regarded as an autoimmune disease in which antibodies are produced against the acetylcholine receptors. Concomitant occurrence of an abnormal thymus gland in patients with the disease is frequently seen (17). Furthermore the disease has been described in dogs and cats, and in association with thymomas similar to what happens in humans (18, 19). Myasthenia gravis has also been reported to be associated with thyroid disease (20, 21), which is also occurring in excess in this cohort. Hence it is not unreasonable to suspect that an infective agent can be involved in this disease. A similar situation exists for anterior horn disease, of which amyotropic lateral sclerosis (ALS) also known as motor neurone disease or Lou Gehrig's disease, is a subtype. The cause is unknown, but an infective or autoimmune process is one of the candidates for an etiological role. Enteroviruses have been hypothesized because of the tropism of polio virus for motor neurons (22), and the gastrointestinal route of infection would fit the link with ingestion of poultry products, including eggs. Similarly, retroviruses are also candidates because motor neuron syndromes are associated with HTLV and HIV infections (22). Respiratory syncytial virus has also been linked to anterior horn cell disease (23). It has also been hypothesized that the high prevalence of the disease in residents of Guam may be due to ingestion of food contaminated with b-methylaminoalanine produced by a cyanobacteria (24). It is interesting that a ten-fold increased risk of death from schizophrenia was observed in this poultry cohort, but it was based on only a single case. Similarly, the SMR for the category other diseases of the spinal cord in the entire poultry cohort, (also based on a single case) was 6.8. These findings are perhaps providing the first clues that cases of some of the neurological diseases that occur in the general population may owe their origin to the presence of transmissible agents present in animals and animal products used for food, such as poultry. The findings are also consistent with the recent report of an outbreak of progressive inflammatory neuropathy among swine slaughterhouse workers in a plant in Minnesota, illustrating that neurological diseases are being caused by working in similar environments in the meat and poultry industries (25).

An infectious etiology can also be linked to the excess of other diseases of the kidney, and peritonitis seen in the cohort. It is interesting that it appears that non-malignant disease of the esophagus may be occurring in excess in the cohort, since an excess of cancer of the esophagus has also been observed in the cohort as well (manuscript submitted), suggesting that the cancer may have been preceded by a pre-malignant lesion.

The increased risk of death of ischemic heart disease appears confined to white women while the increased risk for hypertensive disease appears confined to white men. The reason for this is not known at this time, and further follow-up may throw light on this issue. Similarly, we have no explanation for the deficit of deaths from intracerebral hemorrhage.

The poultry cohort was significantly younger than the control group, 47.2% were born between 1870-1940 as compared with 67.8% of controls. Thus strictly speaking the cause-specific SMRs cannot be directly compared across the poultry group and the control group, hence we will only refer to this control group informally. It is interesting to note that four deaths from anterior horn cell disease occurred in the poultry cohort while none occurred in the control group which was much older and larger in size than the poultry group, and had five years longer follow-up. Similarly two deaths from myasthenia gravis occurred in the poultry cohort while only one death was recorded in the control group. Also, for deaths from senile and pre-senile psychotic conditions (that includes Alzheimer's disease) while there was an excess in nonwhite females, a statistically significant deficit was recorded in the control group, and while one death each from schizophrenia and other diseases of the spinal cord was recorded in the poultry group as a whole (SMR =10.3, SMR=6.8, respectively), no death was recorded in the control group for these conditions. This study also confirms the reported association between myasthenia gravis and thyroid disease. These results therefore strongly suggest that the findings of excess occurrence of these neurological conditions in the poultry group are probably real. The same can also be said to a lesser degree (because of the need to control for confounding factors) for the other conditions that were significantly elevated in the poultry group but not in the control group (diabetes, hypertensive disease, ischemic heart disease, diseases of the esophagus, peritonitis) or the risk was much higher in the poultry group than in the control group (certain zoonotic bacterial diseases, helminthiasis). It is pertinent to note that the control group included a subset of workers engaged in oyster shocking, an occupational group with a possible pre-disposition to infection because of frequent cuts and injury to the skin associated with this job, and from being exposed to concentrated amounts of microorganisms present in oysters because of the filtering action of these shell fish. Thus it may not be unexpected that the control group also demonstrates some excess of deaths from infections.

The quality of record keeping in the Baltimore Meatcutters Union from which this poultry cohort was originally derived was exceptional, to the extent that every subject who had ever applied to the union had a record, and this was independently checked by us by matching application slips with union dues records. Thus selection bias is not an issue that could possibly explain the findings. In the analysis, persons lost to follow-up were assumed to be alive at the end of study – thus the SMRs reported are an underestimation of the true risks. It is possible that chance could explain some of the findings because of the small number of deaths involved in some cases, and the large number of comparisons made. However, in several instances (certain zoonotic bacterial diseases; helminthiasis; myasthenia gravis, for example) the increased risks observed particularly in certain subgroups were extremely high suggesting a causal association. Furthermore, as mentioned above, the causes of death from neurological diseases that were observed to be occurring in excess in the poultry cohort were not observed to be in excess in the control group that was much larger, older, and had longer follow-up.

In conclusion, the findings in this study are uniquely interesting. However, the retrospective cohort design that was used in the study is not suitable to examine which specific occupational exposure(s) is responsible, nor was there opportunity to control for non-occupational confounding factors. The logical next step is to conduct nested case-control studies that will provide the opportunity to examine the role of candidate exposures in greater detail while controlling for occupational and non-occupational confounding factors. In spite of this limitation, the findings are nevertheless important, and most probably present what could very well be the first clues that some neurological and other diseases in humans may be caused as a result of exposure to transmissible agents present in food animals and their products, as previously hypothesized for cancers and other chronic diseases (26).

B. THE PILOT CASE-COHORT STUDY

This preliminary case-cohort study was conducted simultaneously while data collection for the above cohort mortality study was in progress. Hence it was not possible to define cases for the case-cohort study from the cohort mortality study, as it was not known at that time which cancer sites would be in excess in this new cohort mortality study. Therefore selection of the cancer sites that were used as cases for the pilot study was based on six cancer sites observed to be occurring in excess in previous follow-ups of the Baltimore and Missouri cohorts (Johnson et al 1986; Johnson et al 1997; Metayer et al, 1999); Netto et al 2003). These sites were cancers of the lung, esophagus, liver, pancreas, rectum/recto-sigmoid junction/anus, and tumors of the hemopoietic/lymphatic systems (lymphoma, lymphatic leukemia, myeloid stem cell tumors (myeloid leukemia, monocytic leukemia and erythrocytic leukemia), and multiple myeloma)), and they constitute the cancers of interest in the pilot case-cohort study. Cancer of the rectum was excluded from the analysis because there were only 4 deaths from this cause.

The base population from which cases and controls (the subcohort) are derived for this pilot study consists of the subset of the entire cohort of poultry workers and controls who were alive as of January 1, 1990 (N= 43,904 subjects). They were followed up for mortality from 1/1/90 to 2003 and lost subjects were assumed to be alive at the end of 2003. Thus this subset was essentially a closed cohort. Cases were defined as all subjects alive on 1/1/90 who died of a cancer of interest between 1/1/90 to 12/31/2003 (N= 1,126). The control group (the subcohort) consisted of 2,000 subjects who were randomly sampled from the base population of 43,904 subjects alive on 1/1/90. Such a closed cohort is suitable for estimating a risk ratio or cumulative incidence ratio.

Because of the pilot nature of the study, a vigorous or exhaustive attempt was not pursued to trace subjects. Tracing methods consisted of simply looking up the location of the plant, or company, or union the study subject was associated with, and look for the study subject's name in a local directory for that location. We had obtained computer discs of listing of names and telephone numbers from PowerFinder & Sales Leads *info*USA discs-Version 5.2. telephone directory company that covered the entire population in States in which study subjects were derived. All persons with a given name in that location were called until our study subject was identified. For deceased subjects we relied mainly on internet sources such as Public Eye and Ancestry.com to provide an address or phone number to be used for tracing. For deceased subjects not traced by the National Death Index and for whom we had to retrieve their death certificates from State Department of Vital Records to determine cause of death for the cohort mortality study, information on address of study subject and next-of-kin present in the death certificate was used to trace the subject or their next-of-kin using the same procedure. Once contact was made with the right person, the next-of-kin of cases was administered a questionnaire over the phone and provided information on the cases, since all the cases were deceased. Similarly, the next-of-kin of deceased subjects in the control group completed the questionnaire for the deceased subject. Live controls were administered the questionnaire directly. To evaluate the reliability of responses from proxies, the questionnaire was administered to both the live controls and their next-of-kin in a small subset of seven controls. We are currently identifying those questions for which there was discrepancy in the response given by the live study subject and that given by their next-of-kin. Results obtained for these questions will be invalid and the questions will be dropped or modified in future use of the questionnaire. On average the questionnaire took between 40 minutes to an hour to administer. Out of 1,126 cases of the six cancer sites eligible for inclusion in the case-cohort pilot study, 374 (33%) were successfully traced. Of the 374 cases traced, we obtained an interview for 300 (80%) of them. Similarly of 2,000 controls eligible, we attempted to trace 1555 (meaning at least one telephone call was made), of which 214 (14%) were traced, and of those traced, 169 (79%) provided an interview. Thus once individuals were traced, response rates for completing the questionnaire were quite good for both cases and controls. The superior tracing rate for cases was primarily because their death certificates provided information on the informant, the mother and father's name, the place of death, and addresses, while this source of information was not available for controls the vast majority of whom were alive. Also, because of time constraints more time was spent on trying to trace and interview cases than controls.

1) Statistical Analyses for Pilot Case-Cohort Study

For the analysis since this is a preliminary study, we treated the case-cohort study as a case-control study in which the parameter of interest is the odds ratio which is directly equivalent to the risk ratio without any need for the rare disease assumption, since our control group is a random sample of the base population (Rothman & Greenland, 1998). Other methods of analyzing case-cohort data are available such as using the Cox proportional hazard method with the rate ratio as the parameter of interest, but we chose to estimate the risk ratio for simplicity in this preliminary study. Crude odds ratios as well as Mantel-Haenszel (M-H) adjusted odds ratios adjusting only for tobacco smoking because of the low power of the pilot study were estimated. Logistic regression methods were also used to estimate odds ratios controlling for smoking (results not shown because similar to the M-H results). The numbers of cases interviewed for each of the six cancers investigated are given in Table 4. However, to date we have only analyzed the data for cancers of the lung (N= 127 interviewed), pancreas (N=23 interviewed) and liver (N=10 interviewed).

Table 4. Numbers of Cases Interviewed in the Pilot Case-Cohort Study of Six Cancer Sites using a Base Population of Workers alive as of 01/01/90

Cancer Type	N0. of Cases Selected	No. of Cases Traced	No. of Cases Interviewed
Trachea, Bronchus & Lung (ICD 162, C33, 34)	552		133
Esophagus	36		6
Liver & Intrahepatic Bile Ducts (ICD 155, C22)	49		10
Pancreas (ICD 157, C25	87		23
Hemopoietic & Lymphatic Systems (ICD 200, 202-208, C82-C96))	158		45
Rectum/recto-sigmoid junction/ anus	25		4

2) Results & Discussion

In Table 5 the results for the M-H smoking-adjusted odds ratio are given. As can be seen, several occupational tasks as well as non-occupational factors were identified as risk factors for the three cancer sites.

a) Lung Cancer - It is seen that the risks for tasks/activities associated with the highest exposure to transmissible agents viz, catching live chickens, and killing chickens were almost statistically significantly elevated; contact with blood was slightly increased but not significant. Working in stockyards where exposure to live cattle, pigs, sheep occurred was associated with a statistically significant increased risk of lung cancer. This finding confirms previous findings of ours (Johnson, 1991) and others (Coggon et al, 1989). However, because of the small sample size it is not possible to determine if the potential risks associated with catching live chickens and killing chickens is independent of the much higher risk associated with contact with live cattle, pigs, sheep in stockyards. A slightly elevated risk for smoking poultry was observed, but it was not statistically significant. There was no elevated risk observed for the other potentially carcinogenic exposures in the poultry industry, viz., cooking poultry, curing poultry, or using the wrapping machine. It is reassuring that the findings for non-occupational exposures are consistent with those reported in the literature: 1) smoking was a strong risk factor for lung cancer; 2) the risk for working in gasoline stations or gasoline storage facilities (exposure to gasoline and gasoline exhausts) was elevated though not significant. Warts on the body but not on the hands and legs was a very strong risk factor for lung cancer, and this may suggest that certain subtypes of papilloma virus found in this area but in other parts of the body may be a risk factor for lung cancer. Eating salted meat and cirrhosis of the liver were significantly elevated with lung cancer risk. We do not have any explanations for these associations, but exposure to nitrosamines associated with salted food products may be a related cause, since it is known that experimentally, oral intake of nitrosamines can induce lung cancer in animals.

b) Cancer of the Pancreas

The risks for tasks/activities associated with the highest exposure to transmissible agents viz, catching live chickens, and killing chickens were statistically significantly elevated. Use of the wrapping machine was associated with a slight increased risk, but this was not statistically significant. There was not sufficient data to investigate curing and smoking of poultry. An almost 4-fold risk for living in farms where sheep and goats were raised was observed, but the significance of this is unknown at the moment, since the sample size prohibits more detailed exploration. The 2-fold increased risk due to tobacco smoking and that associated with manufacture of dyes are consistent with the literature, as is pancreatitis. Salted meat was observed to be a significant risk factor, but to our knowledge this has not been reported before for cancer of the pancreas.

c) Cancer of the Liver

As for lung cancer and pancreatic cancers, killing of poultry was a strong statistically significant risk factor for liver cancer, as was killing of sheep. Smoking of poultry was also a strong significant risk factor. Data were insufficient to investigate the wrapping machine and curing of meat. Reassuringly, the important non-occupational established causes and risk factors of liver cancer hepatitis B infection, cirrhosis, and aflatoxin were also confirmed in this study, as seen for the odds ratios obtained for hepatitis, cirrhosis and eating of large quantities of peanuts. The findings for infectious mononucleosis and liver cancer appear new, and may be due to the fact that this has not been investigated before. Or may be a chance finding because of small numbers. Thus the non-poultry findings for cancers of the lung, pancreas, and liver in this very small pilot case-cohort study are remarkably consistent with the risk factors reported for these cancers in the literature, thus reinforcing confidence in the validity of the methods employed. The small sample sizes preclude more detailed analysis of the occupational exposures, e.g. it would be interesting to see if the increased risks associated with killing poultry and contact with live poultry persist after controlling for killing or contact with other live animals such as cattle, pigs and sheep, and vice versa.

We were able to interview 7 live control subjects as well as administering the questionnaire to their next-of-kin to provide the same information on the 7 study subjects. We are in the process of comparing the responses for each of the 646 questions in the questionnaire for these two sources. The purpose is to provide some insight as to how well proxy responses are surrogates for responses for live study subjects themselves. Of the 245 direct questions in the questionnaire for which a dichotomous response is required (Yes/No), the agreement between the study subject and his/her proxy responses for the seven pairs was 100% for 44% of the questions; 80-99% for 30% of the questions; 60-79% for 18% of the questions; 50-59% for 4% of the questions; and < 50% for 4% of the questions. Obviously 7 pairs of interviews is too small for the information provided to be definitive, however, these results are most encouraging.

Importantly, the findings of the pilot study indicate that it is feasible to conduct a full blown case-cohort study and that such a study has the potential of providing valuable information even for a rare cancer site with as little as only 10 cases as observed for liver cancer in this pilot study. Similarly quite useful information was provided for cancer of the pancreas even though there were only 23 cases.

Analysis of the findings for tumors of the hemopoietic/lymphatic systems still needs to be conducted, and will begin shortly. Cases of the other two sites esophagus (N=6 interviewed) and rectum (N=4 interviewed) are too few for any meaningful results to be obtained and thus will not be analyzed.

Table 5. Smoking Adjusted Odds Ratios for Cancers of the Lung, Pancreas and Liver

Risk Factor	**Cancer of Lung N=133**	**Cancer of Pancreas N=24**	**Cancer of Liver N=10**	**Risk Factor**	**Cancer of Lung N=133**	**Cancer of Pancreas N=24**	**Cancer of Liver N=10**
Exposure to Poultry Transmissible Agents				**Non-Occupational Risk Factors**			
Kill Chickens	2.4 (0.9-6.7)	5.1 (1.9-13.4)	4.5 (1.1, 18.6)	Did he or she Ever Smoke Tobacco	***7.5 (3.8-14.8)***	*2.1 (0.7-6.4)*	*0.5 (0.2-1.7)*
Contact with Blood	1.3 (0.8, 2.3)	1.6 (0.7-4.0)	1.0 (0.3-3.9)	Infectious mononucleosis	1.9 (0.2-21.1)	-	13.7 (1.3-142.1)
Catch live Chickens	1.9 (0.9-4.0)	2.8 (1.o-7.6)	0.8 (0.1-6.7)	Hepatitis	0.6 (0.2-2.1)	-	10.2 (2.3-44.5)
Worked in a Veterinary clinic/hospital where birds are treated	-	13.8 (0.8-35.1)	-	Cirrhosis	7.7 (1.0-57.4)	1.2 (0.2-9.5)	6.4 (1.3-35.9)
Exposure to Smoke in Smokehouse							
Smoked Poultry	1.5 (0.2-11.8)	-	12.5 (1.1-148.9)	Ate Peanuts a lot	1.2 (0.6-2.1)	1,3 (0.5-3.4)	6.5 (1.6-26.5)
Exposure to Fumes from Wrapping Machine				Nuts	**0.8 (0.5-1.3)**	1.4 (0.6-3.8)	6.6 (0.8-53.4)
Used Wrapping Machine	0.7 (0.3-1.6)	1.5 (0.4-5.4)	-	Warts on body	16.0 (2.9-87.4)	-	-
Exposure to non-Poultry Transmissible Agents in Food Animals (Cattle, Sheep or Goat)				Ate Salted Meat	2.0 (1.2-3.5)	2.7 (1.0-7.4)	1.0 (0.3-3.7)
Stockyard where live animals are held	6.5 (1.6-26.7)	0.8 (0.1-6.3)	2.6 (0.3-25.6)	Inflammation of Pancreas	44.2 + (0.9-2263)	17.3 (5.9-50.3)	-
Farm Where Sheep/goats raised	0.9 (0.3-2.7)	3.9 (1.2-12.5)	-				
Ever Kill sheep	0.4 (0.0-4.5)	-	10.9 (1.1-106.1)				
Curing Meat	0.8 (0.2-4.0)	-	-				
Other Occupational Exposures Outside Poultry & Meat Industries							
Worked Where Dyes Made or Used	1.8 (0.5-7.2)	5.8 (1.7-19.8)	-				
Gasoline station/storage	2.0 (0.9-4.4)	0.7 (0.3-1.3)	1.1 (0.1-9.6)				

Italics for tobacco smoking is unadjusted, as smoking adjusted results do not apply

+ Among non-smokers there was no pancreatitis in liver cancer patients; in smokers there was no pancreatitis in controls, so both strata had zeros.

Conclusion

The results of the mortality study of the Baltimore cohort indicates that workers in poultry slaughtering/processing plants are at increased risk of dying from a variety of diseases, including certain cancers, neurological diseases, cardiovascular diseases, diseases of the urinary and gastrointestinal systems, and other diseases such as zoonotic bacterial diseases and helminthiasis. It is hypothesized that given this pattern of disease occurrence, occupational exposure to transmissible agents present in food animals and their raw products is the prime candidate that may be responsible for the excess occurrence of these diseases, although the role of other candidate occupational exposures need to be investigated using more suitable designs such as a nested case-control or cohprt study. More detailed analysis of the Baltimore cohort is in progress. Analysis of the Missouri and Pension Fund cohorts is also in progress, and it will be interesting to see to what extent these two other cohorts will confirm the findings for the Baltimore cohort.

The findings of the small pilot case-cohort study are available for cancers of the lung, pancreas and liver, while analysis for tumors of the hemopoietic/lymphatic systems will be commence shortly. This study confirms that transmissible agents are probably responsible for the excess risk of cancers of the lung, pancreas and liver observed in the Baltimore cohort study, and identifies workers who are involved in slaughtering activities where exposure to these agents is highest as also having the highest risk of dying from these three cancer sites. In addition, for liver cancer only smoking of poultry was identified as a possible important risk factor. Most reassuringly, this small study remarkably confirmed the important established risk factors for lung, pancreas and liver cancers. The study was too small to investigate other occupational exposures such as exposure to fumes during wrapping, etc., but it does not appear from the results thus far that curing of poultry is associated with any increased risk of dying from the cancers investigated.

It is highly recommended that these cohorts are very important and detailed studies should continue as they hold great promise for identifying the causes of major chronic diseases in the occupational and general populations.

PUBLICATIONS

Faramawi MF, Johnson ES, Fry W, Sall S, Zhou Y. Consumption of different types of meat and the risk of renal cancer: Meta-analysis of observational studies. **Cancer Causes Control** (Springer Science) 10.1007/s10552-006-0104-9. Tuesday January 23, 2007. Hard Copy 18(2): 125-133, 2007. **This meta-analysis of all published studies in the literature confirms an earlier finding of excess of kidney cancer in the poultry workers in the Baltimore cohort.**

Johnson ES, Zhou Y. Noncancer mortality in supermarket meat workers. **J Occup Environ Med** – 49(8): 846-852, 2007. **The software and US mortality rates purchased for this project were first tested on data on a cohort of workers exposed to cattle, pigs and sheep, which had not been published before. This study also found excess of certain cancers in these workers also.**

Johnson ES, Zhou Y, Sall M, El Faramawi M, Shah N, Christopher A, Lewis N. Non-malignant Mortality in Meat Workers - A Model for Studying the Role of Zoonotic Transmissible Agents in Non-malignant Chronic Diseases in Humans. **OEM Online First**, published on June 29, 2007as 10.1136/oem.2006.030825 – **Occup Environ Med** 2007. **The software and US mortality rates purchased for this project were first tested on data on a cohort of workers exposed to cattle, pigs and sheep, which had not been published before. This study also found excess of certain non-malignant diseases in these workers also.**

Johnson ES. Mortality Update of the Baltimore Union Poultry Cohort – Non-malignant Diseases. **Am J Epidemiol** Submitted 2008. **This manuscript is a report of the main findings for the Baltimore cohort in the funded project showing excess of neurological, cardiovascular and urinary non-malignant diseases in these poultry workers.**

Johnson ES, Zhou Y, Yau CL, Prabhakar D, Preacely N. Mortality from Malignant Diseases - Update of the Baltimore Union Poultry Cohort. **Int J Epidemiol** Submitted 2008. **This manuscript is a report of the main findings for the Baltimore cohort in the funded project confirming the excess of certain cancers in workers in poultry slaughtering/processing plants.**

<u>DrPH Dissertation</u>
Nikiconia Preacely: [2008] Lung cancer risk among poultry workers: a pilot study. **This was a pilot case-cohort study to investigate 1) whether a full-blown case-cohort study in this cohort is feasible in future, and 2) to obtain preliminary information on which specific occupational exposures are responsible if at all for the excess occurrence of lung cancer observed in poultry workers in the cohort mortality studies, while controlling for confounding factors such as smoking. This study indicates that a full-blown case-cohort study is feasible and will provide important information. The study also confirmed that the excess of lung cancer in poultry workers is not due to confounding from tobacco smoking. Rather it identified exposure to live animals and slaughtering activities as the main occupational risk factors for lung cancer occurrence in poultry slaughtering/processing plants.**

In addition to these, several manuscripts (about 10-14 are in preparation).

INCLUSION OF GENDER & MINORITY STUDY SUBJECTS

The racial and sex distributions of the study population reflect the respective distributions that prevail in the corresponding workforce in the geographic area. Thus all workers in the poultry industry belonging to these unions are studied irrespective of racial and sex distributions. The Baltimore poultry population is 66% black, and 67% males. The Missouri poultry population is over 92% white, and 22% males. The Chicago cohort is 36% females and it is estimated that at least 30% are black. This is an occupational study, hence children are not included.

INCLUSION OF CHILDREN

This was an occupational study with the youngest subject more than 40 years old at the time of data collection.

MATERIALS AVAILABLE FOR OTHER INVESTIGATORS

There are none available at the moment since analysis of the data is in progress and will continue for he next two years. When all analyses are complete and all manuscripts published emanating from the project have been published, the data without personal identifiers could be made available to other investigators on request provided adequate notice is given.

b) **FINAL FINANCIAL STATUS REPORT**
See attachment

c) FINAL INVENTION STATEMENT
There was no invention emanating from this project.