these subjects ranged from 3.5 to 90 ng/kg and were negatively sociated with AhR mRNA in unstimulated peripheral blood mononuear cells (p=0.03). When mitogen-induced lymphocytes were culred with 10nM TCDD, all AhR-dependent genes were induced 1.2 to -fold. In these cells, plasma TCDD was associated with decreased ROD activity. In addition, there was a strong positive correlation tween AhR and CYP1A1 expression (p=0.001) and between AhR d CYP1B1 expression (p=0.006). CYP1A1 expression was also rongly correlated with EROD activity (p=0.001). Four CYP1B1 polyorphisms and related haplotypes were studied. Both CYP1B1 genoypes, particularly the CYP1B1*3 allele, and CYP1B1 haplotypes sigficantly reduced CYP1B1 expression inducibility after cell culture with vitro TCDD (p=0.04, t-test comparing CYP1B1 expression in the onsensus genotype versus the expression in subjects with any YP1B1 genotype variant; and chisquare=10.37, p=0.006, Pearson's nalysis comparing the inducibility of CYP1B1 expression between all riant CYP1B1 haplotypes versus the CYP1B1*1 haplotype). CYP1A1, STM1, and GSTT1 genotypes were not significantly associated with YP1A1 expression and EROD activity. The analysis of the expression dioxin-inducible genes involved in carcinogenesis may help in detrmining dose-response relationships for human exposure to dioxin in vo and in assessing the variability of human response, which may dicate the presence of subjects more susceptible to disease as a sult of such exposures. We are grateful to Andrew Bergen , PhD, Core Genotyping Facility, NCI, for his contribution in the haplotype analysis.

#6399 ***Myb*-DNA binding inhibited by herbicides *in vitro*.** Larry W. Riggs and Jimmy D. Page. *Saint Louis University School of Public Health, St. Louis, MO and Biacore, Inc., Piscataway, NJ.*

Introduction: Although some herbicides are potential chemical carcinogens and epidemiologic evidence suggests that they are associated with lymphomas, the peripheral blood lymphocytes of people exposed to some herbicide show no evidence of chromosomal damage or mutations, but may show changes in cell cycle kinetics. To explore a potential pathway to herbicide-induced cell cycle deregulation, we examined changes in molecular interactions between *Myb*, a transactivating oncoprotein that regulates G1/S transition in dividing cells, and its DNA consensus-sequence binding site. *Methods* : We used electrophoresis mobility shift assays (EMSAs) to separate *Myb*-bound and free DNA from 30μl assays containing 1.0μg of custom 50mer oligonucleotides with a single *Myb* binding site sequence (AACGG), 2 ng of *Myb*, and varying dilutions ($1:10^2$ - $1:10^8$ assay dilution) of commercially available herbicides in phosphate buffered saline incubated overnight at 2 °C. Gels were stained with a fluorescent nucleic acid stain, exposed to ultraviolet radiation, and band luminosity was quantified by image analysis. Sigmoidal regression models were used to predict binding throughout each herbicide's dilution range. Using surface plasmon resonance (SPR) spectroscopy to observe herbicide-specific influences on dynamic *Myb*-DNA molecular interactions, we measured and compared association (k_a), dissociation (k_d), and equilibrium (K_D) rate constants of *Myb* and our custom oligonucleotide with herbicides diluted 1:500) and without herbicide present. *Results* : Image analysis of EMSA gels showed that 2,4-DLV4® decreased *Myb*-DNA binding at a final assay dilution of $1:10^5$, Tordon RTU® decreased *Myb*-DNA binding at a $1:10^6$ final assay dilution, and Roundup® decreased *Myb*-DNA binding following a $1:10^3$ final assay dilution. SPR analysis of *Myb*-DNA interactions showed that the three herbicides modified the k_a, k_d, or K_D rate constants when present at a 1:500 assay dilution. *Conclusion* : Commercially available 2,4-D LV4®, Tordon RTU®, and Roundup® may modify *Myb*-DNA molecular interactions *in vitro* at concentrations ranging from $1:10^3$ to $1:10^6$ assay dilution.

#6400 Farm exposure to individual pesticides and glioma in men. Avima M. Ruder, Martha A. Waters, Tania Carreon, Mary Ann Butler, Geoffrey M. Calvert, Karen E. Davis-King, Paul A. Schulte, Wayne T. Sanderson, Elizabeth M. Ward, L. Barbara Connally, Ellen F. Heineman, Jack S. Mandel, Roscoe F. Morton, Douglas J. Reding, Kenneth R. Rosenman, and Glenn Talaska. *National Institute for Occupational Safety and Health, Cincinnati, OH, National Cancer Institute, Rockville, MD, University of Minnesota, Minneapolis, MN, Mercy Medical Center, Des Moines, IA, Marshfield Clinic National Farm Med. Ctr., Marshfield, WI, Michigan State University, East Lansing, MI, and University of Cincinnati, Cincinnati, OH.*

An excess incidence of brain cancer in farmers has been noted in several studies. The Brain Cancer Collaborative Study Group conducted the Upper Midwest Health Study to evaluate associations between rural exposures and brain cancers among adult (18-80) male and female rural residents in Iowa, Michigan, Minnesota and Wisconsin, where brain cancer incidence is significantly elevated. Histologically confirmed intracranial glioma cases (458 men) diagnosed January 1, 1995, through January 31, 1997, were identified from hospitals, medical practices, and cancer registries. Controls (648 men) were stratified samples of licensed drivers (ages 18-64) and Health Care Finance Administration enrollees (ages 65-80) residing in rural counties of each state. In-person interviews with participants or proxies collected farm, occupational, and other exposure information. Participants who lived on a farm where a pesticide was used were classified as exposed to that pesticide; those who reported personally handling a pesticide on the farm were classified as users. A NIOSH reference database, with over 800 trade names whose active ingredients have been identified, was used to convert pesticide trade name responses to generics. The frequency of farm use of generics was used to identify pesticides to which at least 100 participants (men and women) reported exposure. Multivariate logistic regressions controlled for farm residence and for age since controls were older. Those exposed to or using farm pesticides were compared with the 128 controls and 125 cases who had no farm, home and garden, or occupational pesticide exposure. Exposure to any farm pesticide was associated with lower glioma risk: adjusted odds ratio (OR) 0.54, 95% confidence interval (CI), 0.36-0.83. There was no association between farm residents' exposure to alachlor, cyanazine, diazinon, dicamba, glyphosate, metolachlor, pendimethalin, or trifluralin, and glioma risk. There were negative statistically significant associations between glioma risk and farm residents' exposure to 2,4-D, atrazine, DDT, and malathion. Use of any farm pesticide also was associated with lower glioma risk: OR 0.51, CI, 0.33-0.80. Personal use of pesticides on the farm was significantly lower among cases than controls for 2,4-D, alachlor, atrazine, cyanazine DDT, dicamba, malathion, and metolachlor. Results for analyses excluding proxy respondents (47% of cases) did not differ significantly. Evidence has been shown for pesticides crossing the blood-brain barrier and for pesticide central nervous system neurotoxicity. However the evidence for pesticide carcinogenicity in the brain is not strong. In our study, no positive association of farm pesticide exposure or use and glioma risk was found. Other farm exposures, which will be analyzed in future papers, may explain the excess brain cancer risk seen in previous studies of rural residents.

#R6401 Farm exposure to pesticides and glioma in women. Tania Carreon, Mary Ann Butler, Avima M. Ruder, Martha A. Waters, Karen E. Davis-King, Geoffrey M. Calvert, Paul A. Schulte, L. Barbara Connally, Elizabeth M. Ward, Wayne T. Sanderson, Ellen F. Heineman, Jack S. Mandel, Roscoe F. Morton, Douglas J. Reding, Kenneth R. Rosenman, and Glenn Talaska. *National Institute for Occupational Safety and Health, Cincinnati, OH, National Cancer Institute, Rockville, MD, University of Minnesota, Minneapolis, MN, Mercy Medical Center, Des Moines, IA, Marshfield Clinic, Marshfield, WI, Michigan State University, East Lansing, MI, and University of Cincinnati, Cincinnati, OH.*

An excess incidence of brain cancer in male farmers has been noted in several studies, but few studies have focused on women. This study evaluated the association between pesticide exposure and brain cancer among adult (18-80) female rural residents in Iowa, Michigan, Minnesota and Wisconsin, states where brain cancer incidence is significantly elevated. Since hormonal factors may play a role in the development of brain tumors, the effect of pesticides reported as endocrine disruptors was also evaluated. Histologically confirmed intracranial glioma cases (n=341) were identified from hospitals and medical practices. Controls (n=528) were stratified samples of rural residents who were licensed drivers (ages 18-64) and Health Care Finance Administration enrollees (ages 65-80). In-person interviews collected farm, occupational and other exposure information. Participants exposed to pesticides resided on farms where pesticides were used; participants who used pesticides personally handled them. A National Institute for Occupational Safety and Health database was used to convert pesticide trade name responses to generics. Pesticides to which ≥100 participants (either gender) reported exposure were identified. Logistic regression models adjusted for farm residence and

age, using as reference group 156 cases and 201 controls who had no farm, home and garden, or occupational pesticide exposure. Women for whom exposure to any pesticide on the farm was reported had no higher risk of glioma (adjusted odds ratio [OR]=0.9, 95% confidence interval [CI] 0.56-1.34), but lower glioma risk was associated with use of any farm pesticide (OR=0.5, CI 0.25-0.87). No association with glioma was observed for exposure to or use of arsenical pesticides, botanical pesticides, carbamates, chloroacetanilides, dinitroanilines, dinitrophenols, inorganic pesticides, organochlorines, organothiophosphates, phenoxy pesticides, triazines, or urea-based pesticides. A negative statistically significant association was observed for farm residents' exposure to organophosphates and glioma, but not for personal use. No association was observed between farm residence, exposure to or use of 2,4-D, atrazine, cyanazine, diazinon, dicamba, glyphosate, malathion, metolachlor, pendimethalin, or trifluralin, and glioma risk. Pesticides with reported estrogenic activities, such as DDT and alachlor, did not affect the risk of glioma. Women were less likely than men to have applied pesticides, but more likely to have laundered pesticide-contaminated clothes. Results were not affected by exclusion of proxy responses (43% cases, 3% controls). This is the first population-based case-control study of glioma among rural residents to evaluate the effect of pesticide exposure and work practices in women. No evidence for association of pesticide use and glioma risk was found. Other farm exposures, yet to be analyzed, may explain the excess brain cancer among rural residents.

#R6402 Pesticide exposure and the risk of non-Hodgkin lymphoma by subtype. John J. Spinelli, Leo F. Skinnider, Zenaida U. Abanto, Jeremy D. Hamm, Shirley Fincham, John R. McLaughlin, Helen H. McDuffie, Punam Pahwa, Diane Robson, and James A. Dosman. *BC Cancer Agency, Vancouver, British Columbia, Canada.*

Background: We have previously reported an association between non-Hodgkin lymphoma (NHL) and exposure to phenoxy and dicamba herbicides, carbamate, organophosphorus and organochlorine insecticides, and amide fungicides in a population based case-control study conducted in six Canadian provinces (McDuffie et al, 2001). As NHL is a heterogeneous disease comprised of several distinct histopathological subtypes with prognostic importance, it is of great interest to determine if there is heterogeneity in the associations between the different subtypes of NHL. We examined the odds ratios for NHL and pesticide exposure by histopathological subtype. *Methods:* Males diagnosed with NHL between 1991 and 1994 (n=504) and frequency-matched controls (n=1506) were ascertained. Exposure to pesticides and other risk factors were collected using a mailed questionnaire followed by a telephone interview to assess detailed pesticide exposure. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression controlling for other significant risk factors and stratified for the matching variables age and province. NHL cases were coded using ICD-O-2 by the respective provincial cancer registries, and were re-categorized according to the Working Formulation. Pathological review by an expert pathologist occurred for 61% of cases. For those cases reviewed, there was agreement at the major subtype level (diffuse, follicular, SLL, diffuse small cleaved, other) in 81%; Kappa=0.73 (95%CI=0.66, 0.80). In cases of disagreement, the classification of the expert pathologist was used. Odds ratios associated with specific pesticides were examined in each of three subtype groups; diffuse (41%), follicular (25%) and other and unclassified (34%). *Results:* Heterogeneity in the odds ratios was observed for significant pesticide exposure (greater than 10 hours per year). For significant pesticide exposure, odds ratios for NHL subtypes were OR=1.5 (95%CI=1.0,2.1) for diffuse, OR=0.9 (0.6,1.5) for follicular and OR=1.4 (0.9,2.0) for other and unclassified (p for interaction=0.077). There was little heterogeneity in the odds ratios between subtypes observed for exposure to specific pesticides. *Conclusions:* These results provide no evidence of large variation in risk for exposure to specific pesticides between subtypes of non-Hodgkin lymphoma. (Supported by Health Canada and the British Columbia Health Research Foundation).

#6403 Comparison of male breast cancers in farmers and non-farmers: A review of cases at the Saskatchewan Cancer Agency. Kylie E. Kvinlaug, Helen H. McDuffie, and Punam Pahwa. *Institute of Agricultural Rural and Environmental Health, University of Saskatchewan, Saskatoon, Saskatchewan, Canada.*

The purpose of this study was twofold: 1) To compare whether farmers, due to their implied exposures to pesticides, develop male breast cancer at an earlier age resulting in a more severe form of the disease and shorter survival compared to non-farmers. 2) To characterize all cases of male breast cancer registered at the Saskatchewan Cancer Agency, a population-based registry, between 1932 and December 31st, 2000. All (137) cases of male breast cancer were reviewed at the Saskatchewan Cancer Agency. Ten cases did not meet the criteria and were removed from the study. The remainder were grouped according to occupation (farmer, non-farmer, or unknown). Comparisons between farmers (n=41) and non-farmers (n=54) were made using the independent samples t-test and Chi-squared test. Cox proportional hazard models and Kaplan-Meier survival analysis were used to compare survival within occupational groupings and other variables. The mean age (standard deviation) at diagnosis for all cases was 67.2 (13.3) years. Farmers were diagnosed at an average age of 68.5 (13.5) years compared to 63.0 (11.2) years for non-farmers (p=0.04). There were no statistically significant differences between occupational groups for years of life after diagnosis, maximum tumor dimension, lymph node involvement at diagnosis, or relapse occurrence comparing farmers and non-farmers. Farmers had a median survival of 4.5 years compared to 5.0 years for non-farmers. In regards to cause of death, 17% of farmers and 24% of non-farmers died of breast cancer. The mean maximum tumor dimension in farmers was 2.5 (1.6) cm compared to 2.3 (1.4) cm in non-farmers. Known lymph node involvement at diagnosis occurred in 55% of farmers and 56% of non-farmers. Farmers had more higher staged (stages III and IV) breast cancers than non-farmers at 22% and 6% respectively. However, farmers had fewer diagnoses of other cancers compared to non-farmers (p=0.03). Survival analysis revealed no statistically significant difference in survival between farmers and non-farmers. However, cases who were older at diagnosis, died of male breast cancer, had a higher staged cancer, had a larger tumor, had a relapse, or had a cancer prior to breast cancer all had statistically significant shorter survival times compared to reference cases ($p<0.01$). Multivariate analysis indicated age at diagnosis, maximum tumor dimension, lymph node status at diagnosis, and relapse occurrence were the most significant independent predictors of length of survival (p=0.01 or less). These data did not support the hypothesis that farmers are more likely to be diagnosed at a younger age or with a more severe form of the disease due to their agricultural chemical exposure in comparison to non-farmers. (Supported by the University of Saskatchewan College of Medicine Dean's Fellowship and I.ARE.H.)

#R6404 A modified immuno-enriched ^{32}P-postlabeling method for analysing malondialdehyde derived 1,N^2-propano-deoxyguanosine DNA adducts in human tissue samples. Xin Sun, Helmut Bartsch, and Jagadeesan Nair. *German Cancer Research Center (DKFZ), Heidelberg, Germany.*

The malondialdehyde (MDA) modified DNA adduct, 3-(2-deoxy-β-D-erythro-pentofuranosyl)pyrimido[1,2-A]purin-10(3H)-one (M_1dG) has been detected in human tissues and is considered to be a promising biomarker to estimate lipid peroxidation-induced DNA damage. With the aim to analyse the M_1dG adduct in small amounts of DNA (< 10 μg) and to improve the sensitivity, we have developed an immuno-enriched ^{32}P-postlabeling-HPLC method. The main modifications included the following steps: (i) an optimization of the immuno-enrichment conditions for which a MAb (D 10A1) developed in Vanderbilt University, Nashville, USA (provided by L.J. Marnett) has been used, (ii) a single labeling step of the purified M_1dG to its 5'-monophosphate at pH 6.8, (iii) the addition of O^4-ethylthymidine (O^4-etT) as an internal standard for correcting labeling efficiency and (iv) a pre-purification of the labeled adduct on a PEI minicolumn before HPLC analysis. With this protocol, the percent recovery of M_1dG adduct was found to be ~ 70 ±20; the detection limit in biological samples was ~ 200 amol M_1dG from 10 μg DNA, corresponding to 6 adducts/10^9 nucleotides. In conclusion, our modified method shows a high sensitivity and specificity; when applied to human breast and liver tissue samples, background levels of the M_1dG adduct could be reproducibly detected. This ultrasensitive detection method is suitable for applications in human biomonitoring and molecular epidemiology studies (supported by EU research grant QLK4-CT-2000-00286).

AACR American Association for Cancer Research

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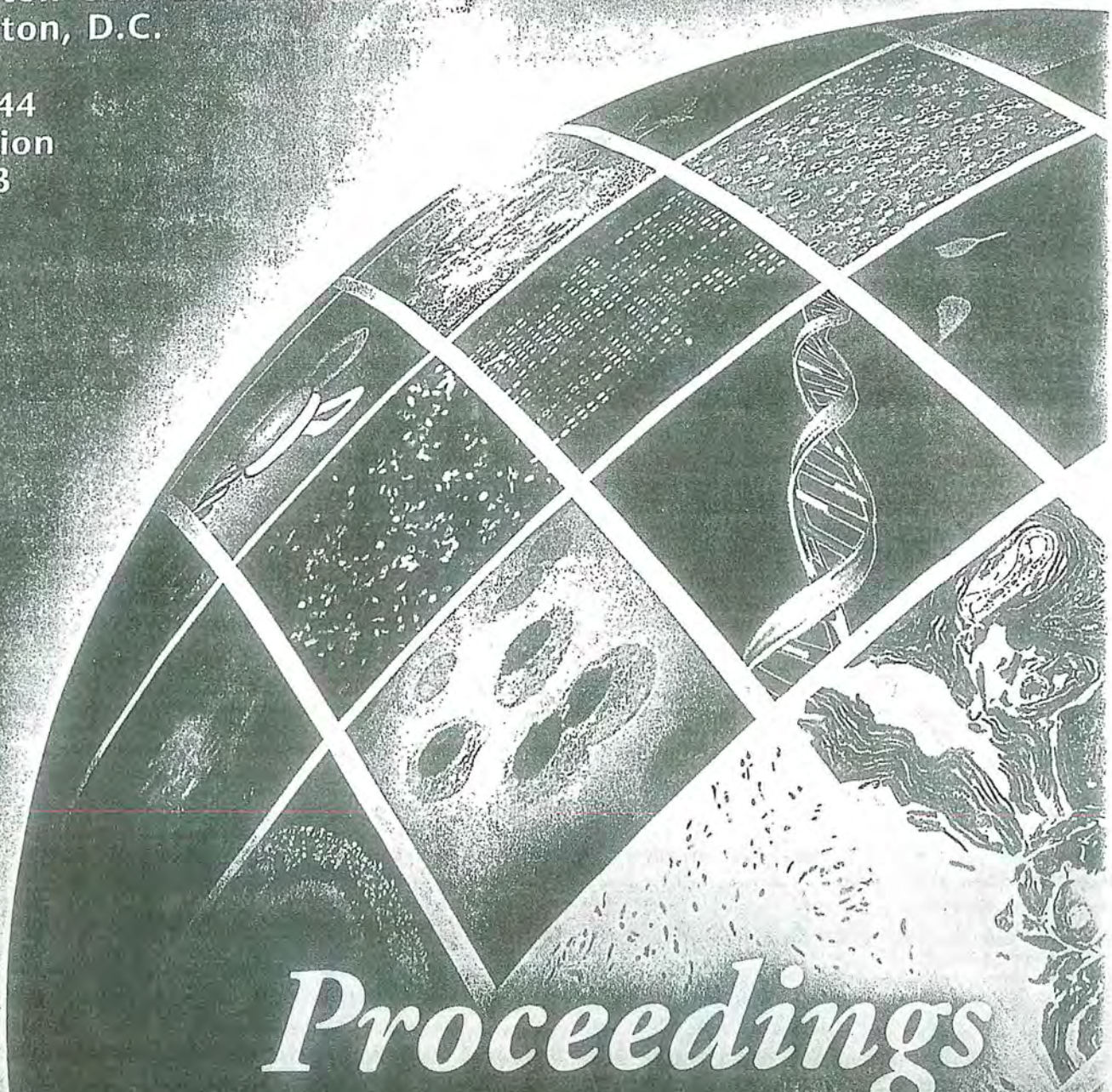
Volume 44
2nd Edition
July 2003



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