2,4-Dichlorophenoxyacetic acid
cancer, incl. epidemiology
PUBMED 2011.09.09

Ricker JM, Mathis DA, Arnold HL. 2010 Jul. An interesting case of iron deficiency anemia. Gastrointest Endosc 72(1):189; discussion 190.

Boers D, Portengen L, Bueno-de-Mesquita HB, Heederik D, Vermeulen R. 2010 Jan. Cause-specific mortality of Dutch chlorophenoxy herbicide manufacturing workers. Occup Environ Med 67(1):24-31.Abstract: OBJECTIVE: A retrospective cohort study was conducted in two chlorophenoxy herbicide manufacturing factories, producing mainly 2,4,5-trichlorophenoxyacetic acid (factory A) and 4-chloro-2-methylphenoxyacetic acid, 4-chloro-2-methylphenoxy propanoic acid and 2,4-dichlorophenoxyacetic acid (factory B). Previously, we have shown elevated risks for mortality and cancer mortality in this cohort. The purpose of the current, third follow-up, is to provide an updated assessment of cause-specific mortality for both factories. METHODS: The study population was defined as all persons working in one of the two factories during 1955-1985 for factory A, or during 1965-1986 for factory B. Analyses were performed using Cox proportional hazard models, using attained age as the timescale. Exposure to phenoxy herbicides and dioxins was expected to be different for factory A and factory B and the factories were therefore analysed separately. RESULTS: Previously reported increased risks for respiratory cancer, non-Hodgkin's lymphoma and ischaemic heart disease in factory A could not be confirmed in the present analysis. However, increased risks were observed for all cancers in both factory A (hazard ratio (HR) 1.31; 95% CI 0.86 to 2.01) and factory B (HR 1.54; 95% CI 1.00 to 2.37). Increased risks for urinary cancers (HR 4.2; 95% CI 0.99 to 17.89) and genital cancers (HR 2.93; 95% CI 0.61 to 14.15) were observed in factory A, consistent with earlier reported results in this population. More detailed analyses showed that this increased risk for urinary and genital cancers in exposed workers was not due to selection of healthy controls and could not be attributed to specific products or departments. CONCLUSION: The results of this study showed only slight increases in cancer mortality risk. The increased risk for urinary cancers is noteworthy, but could not be linked to a specific exposure and needs to be confirmed in similar cohorts.

Schecter A, Needham L, Pavuk M, Michalek J, Colacino J, Ryan J, Papke O, Birnbaum L. 2009 Jul 15. Agent Orange exposure, Vietnam war veterans, and the risk of prostate cancer. Cancer 115(14):3369-71.

Shah SR, Freedland SJ, Aronson WJ, Kane CJ, Presti JC Jr, Amling CL, Terris MK. 2009 May. Exposure to Agent Orange is a significant predictor of prostate-specific antigen (PSA)-based recurrence and a rapid PSA doubling time after radical prostatectomy. BJU Int 103(9):1168-72.Abstract: OBJECTIVE: To investigate and report the clinicopathological characteristics and outcomes after radical prostatectomy (RP) in patients with prostate cancer and previous exposure to Agent Orange (AO), particularly in relationship to race. PATIENTS AND METHODS: In 1495 veterans who had undergone RP the clinicopathological characteristics, biochemical progression rates, and prostate-specific antigen (PSA) doubling time (DT) after recurrence between AO-exposed and unexposed men were compared using logistic and linear regression and Cox proportional hazards analyses, and stratified by race. RESULTS: The 206 (14%) men with AO exposure were more likely to be black ($P = 0.001$), younger ($P < 0.001$), treated more recently ($P < 0.001$), have a higher body mass index ($P = 0.001$), have clinical stage T1 disease ($P < 0.001$), and have lower preoperative PSA levels ($P = 0.001$). After adjusting for several clinical characteristics, AO exposure was not significantly related to adverse pathological features but was significantly associated with biochemical progression risk (relative risk 1.55, 95% confidence interval 1.15-2.09, $P = 0.004$) and shorter PSADT ($P < 0.001$) after recurrence (8.2 vs 18.6 months). When stratified by race, these associations were present and similar in both races, with no significant interaction between race and AO exposure for predicting biochemical recurrence or mean adjusted PSADT (P interaction >0.20). CONCLUSIONS: Patients with AO exposure and treated with RP were more likely to be black, present with lower risk features, have an increased risk of biochemical progression, and shorter PSADT after recurrence. When stratified by race, the association between AO exposure and poor outcomes was present in both races. These findings suggest that among selected men who choose RP, AO exposure might be associated with more aggressive prostate cancer.

Everly L, Merrick GS, Allen ZA, Butler WM, Wallner K, Lief JH, Galbreath RW, Adamovich E. 2009 Jan-Mar.

Prostate cancer control and survival in Vietnam veterans exposed to Agent Orange. Brachytherapy 8(1):57-62. Abstract: BACKGROUND: In this study, we evaluated the impact of Agent Orange exposure on survival in Vietnam Veterans undergoing prostate brachytherapy. METHODS AND MATERIAL: From May 1995 to January 2005, 81 Vietnam veterans (29 with Agent Orange exposure and 52 without) and 433 nonveterans of comparable age (mean age, 58 years) underwent prostate brachytherapy. The mean follow-up was 5.0 years. Biochemical progression-free survival (bPFS) was defined as a prostate-specific antigen (PSA)< or =0.40ng/mL after nadir. Patients with metastatic prostate cancer or hormone refractory disease without obvious metastases who died of any cause were classified as died of prostate cancer. All other deaths were attributed to the immediate cause of death. Multiple parameters were evaluated for impact on survival. RESULTS: At 9 years, Agent Orange-exposed men were least likely to remain biochemically controlled (89.5%, 100%, and 97.2% in Agent Orange-exposed, nonexposed veterans, and nonveterans, respectively, p=0.012). No significant differences in cause-specific (CSS) (p=0.832) or overall survival (OS) (p=0.363) were discerned. In multivariate analysis, CSS was best predicted by Gleason Score and day 0 D(90), whereas Gleason Score, % positive biopsies, and D(90) predicted for bPFS. None of the evaluated parameters predicted for OS, however, a trend was identified for better OS in younger patients and those with a higher D(90). In addition, Agent Orange exposure did not predict for any of the survival parameters. To date, 22 patients have died (metastatic prostate cancer two, second malignancies nine, cardiovascular disease eight, trauma two, and pulmonary one). CONCLUSIONS: In this cohort of prostate brachytherapy patients, Agent Orange exposure did not statistically impact survival in multivariate analysis.

Shah SR, Terris MK. 2008 Nov 1. Editorial comment on: Agent Orange exposure, Vietnam War veterans, and the risk of prostate cancer. Cancer 113(9):2382-4.

Chamie K, DeVere White RW, Lee D, Ok JH, Ellison LM. 2008 Nov 1. Agent Orange exposure, Vietnam War veterans, and the risk of prostate cancer. Cancer 113(9):2464-70. Abstract: BACKGROUND: It has been demonstrated that Agent Orange exposure increases the risk of developing several soft tissue malignancies. Federally funded studies, now nearly a decade old, indicated that there was only a weak association between exposure and the subsequent development of prostate cancer. Because Vietnam War veterans are now entering their 60s, the authors reexamined this association by measuring the relative risk of prostate cancer among a cohort of men who were stratified as either exposed or unexposed to Agent Orange between the years 1962 and 1971 and who were followed during the interval between 1998 and 2006. METHODS: All Vietnam War era veterans who receive their care in the Northern California Veteran Affairs Health System were stratified as either exposed (n=6214) or unexposed (n=6930) to Agent Orange. Strata-specific incidence rates of prostate cancer (International Classification of Diseases, 9th Revision code 185.0) were calculated. Differences in patient and disease characteristics (age, race, smoking history, family history, body mass index, finasteride exposure, prebiopsy prostate-specific antigen (PSA) level, clinical and pathologic stage, and Gleason score) were assessed with chi-square tests, t tests, a Cox proportional hazards model, and multivariate logistic regression. RESULTS: Twice as many exposed men were identified with prostate cancer (239 vs 124 unexposed men, respectively; odds ratio [OR], 2.19; 95% confidence interval [95% CI], 1.75-2.75). This increased risk also was observed in a Cox proportional hazards model from the time of exposure to diagnosis (hazards ratio [HR], 2.87; 95% CI, 2.31-3.57). The mean time from exposure to diagnosis was 407 months. Agent Orange-exposed men were diagnosed at a younger age (59.7 years; 95% CI, 58.9-60.5 years) compared with unexposed men (62.2 years; 95% CI, 60.8-63.6 years), had a 2-fold increase in the proportion of Gleason scores 8 through 10 (21.8%; 95% CI, 16.5%-27%) compared with unexposed men (10.5%; 95% CI, 5%-15.9%), and were more likely to have metastatic disease at presentation than men who were not exposed (13.4%; 95% CI, 9%-17.7%) than unexposed men (4%; 95% CI, 0.5%-7.5%). In univariate analysis, distribution by race, smoking history, body mass index, finasteride exposure, clinical stage, and mean prebiopsy PSA were not statistically different. In a multivariate logistic regression model, Agent Orange was the most important predictor not only of developing prostate cancer but also of high-grade and metastatic disease on presentation. CONCLUSIONS: Individuals who were exposed to Agent Orange had an increased incidence of prostate cancer; developed the disease at a younger age, and had a more aggressive variant than their unexposed counterparts. Consideration should be made to classify this group of individuals as 'high risk,' just like men of African-American heritage and men with a family history of prostate cancer.

Michalek JE, Pavuk M. 2008 Mar. Diabetes and cancer in veterans of Operation Ranch Hand after adjustment for

calendar period, days of spraying, and time spent in Southeast Asia. J Occup Environ Med 50(3):330-40.Abstract: BACKGROUND: The Air Force Health Study was launched in 1980 as part of a Federal effort to resolve the Agent Orange issue. OBJECTIVES: To study diabetes and cancer with additional adjustment for days of spraying, calendar period of service, and time spent in Southeast Asia (SEA). METHODS: This was a longitudinal study of veterans of Operation Ranch Hand, the unit responsible for spraying Agent Orange and other 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-contaminated herbicides in Vietnam from 1962 to 1971. RESULTS: Associations between TCDD and diabetes and between TCDD and cancer in Ranch Hand veterans are strengthened after adjustment for calendar period of service, days of spraying, and, for cancer, time spent in SEA. CONCLUSIONS: Calendar period of service, days of spraying, and time spent in SEA are important confounders in the Air Force Health Study.

Burns CJ, Mahlburg WM, Dutra JP. 2007 Oct. Pesticide exposure among farm workers. Environ Res 105(2):285-6; discussion 287-8 .

Mills PK, Yang RC. 2007 Jun. Agricultural exposures and gastric cancer risk in Hispanic farm workers in California. Environ Res 104(2):282-9.Abstract: Previous studies have indicated that farm workers may be at increased risk of gastric cancer. Meta-analyses, ecological, case-control, and cohort studies suggest that some aspects of the agricultural environment may be implicated in the elevated risk. Hispanic farm workers in California are exposed to a multitude of potentially toxic substances in the work site, including excessive sunlight, fertilizers, diesel fumes, and pesticides. A previous analysis of a cohort of California farm workers who had been members of a farm labor union, the United Farm Workers of America (UFW) found a proportionate cancer incidence ratio for stomach cancer of 1.69 when using the California Hispanic population as the standard. The aim of the current study was to further evaluate associations between gastric cancer and the types of crops and commodities UFW members cultivate and the associated pesticide use as recorded by the California Department of Pesticide Regulation (DPR). We conducted a nested case-control study of gastric cancer embedded in the UFW cohort and identified 100 cases of newly diagnosed gastric cancer between 1988 and 2003. We identified 210 control participants matched on age, gender, ethnicity, and who were known to be alive and resident in California up to the date of the cases' diagnosis. Both stratified analyses and unconditional logistic regression were used to calculate adjusted odds ratios (OR) and 95% confidence intervals (95% CI). Work in the citrus industry was associated with increased gastric cancer (OR=2.88; 95% CI=1.02-8.12) although no other specific crops or commodities were associated with this disease. Working in areas with high use of the phenoxyacetic acid herbicide 2,4-D was associated with gastric cancer (OR=1.85; 95% CI=1.05-3.25); use of the organochlorine insecticide chlordane was also associated with the disease (OR=2.96; 95% CI=1.48-5.94). Gastric cancer was associated with use of the acaricide propargite and the herbicide triflurin (OR=2.86; 95% CI=1.56-5.23 and 1.69, 95% CI=0.99-2.89, respectively). **Gastric cancer in California Hispanic farm workers is associated with work in the citrus fruit industry and among those who work in fields treated with 2,4-D, chlordane, propargite, and trifluin.** These findings may have larger public health implications especially in those areas of the country where these pesticides are heavily used and where they may be found in the ambient atmosphere.

Atallah E, Schiffer CA. 2007 May. Agent Orange, prostate cancer irradiation and acute promyelocyic leukemia (APL): is there a link? Leuk Res 31(5):720-1.

Stone R. 2007 Jan 12. Epidemiology. Agent Orange's bitter harvest. Science 315(5809):176-9.

Miligi L, Costantini AS, Veraldi A, Benvenuti A, Vineis P. 2006 Sep. Cancer and pesticides: an overview and some results of the Italian multicenter case-control study on hematolymphopoietic malignancies. Ann N Y Acad Sci 1076:366-77.Abstract: Exposure to pesticides is recognized as an important environmental risk factor associated with development of cancer. Epidemiological studies, although sometimes contradictory, have linked phenoxy acid herbicides with non-Hodgkin's lymphoma (NHL) and Soft Tissue Sarcoma (STS); organochlorine insecticides with STS, NHL, and leukemia; organophosphorous compounds with NHL and leukemia; and triazine herbicides with ovarian cancer. Exposure assessment is a crucial point in studying the association between cancer and pesticides. In order to investigate the association between hematolymphopoietic malignancies and occupational exposures, including pesticides, a population-based case-control study was carried out in Italy in 11 areas, 9 of which are agricultural or mixed areas. All newly

diagnosed cases of hematolymphopoietic malignancies were collected in a 3-year period (1991-1993). The control group consisted of a random sample of the population residing in each area. The approach to infer exposures in agriculture was based on: the use of an agricultural questionnaire with 24 crop-specific questionnaires; expert agronomists who reviewed the collected information for each subject and translated it into pesticides histories. In total, 1925 cases and 1232 controls were interviewed in the nine agricultural areas. Increased risk was observed for some specific classes of pesticides. Furthermore, a nonstatistically significant increased risk of NHL was observed for subjects who were exposed to phenoxy herbicides not using protective equipment and a significant increased risk for exposure to 2, 4-dichlorophenoxy acetic acid (2,4-D).

Handler S. 2006 Apr. Story short on science. Minn Med 89(4):6-7.

Pavuk M, Michalek JE, Ketchum NS. 2006 Mar. Prostate cancer in US Air Force veterans of the Vietnam war. J Expo Sci Environ Epidemiol 16(2):184-90.SEPAbstract: US Air Force veterans of Operation Ranch Hand sprayed herbicides contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in Vietnam from 1962 to 1971. Comparisons served in Southeast Asia (SEA) during the same time period but did not spray herbicides. Here we investigate a potential association between exposure to TCDD and prostate cancer. Data were available for 2516 veterans (1019 Ranch Hand and 1497 Comparison) who participated in at least one of six physical examinations starting in 1982 and had a measurement of serum TCDD. We assigned Ranch Hands to two exposure categories: Lower and Higher, based on their median 20-year cumulative TCDD level. In total, 81 Comparison and 59 Ranch Hand prostate cancers were identified between 1 January 1982 and 31 December 2003. We found no overall increase in the risk of prostate cancer in Ranch Hand veterans versus the Comparisons. There was a positive association in Ranch Hand veterans in the Higher TCDD category who served in SEA before 1969 (RR=2.27, 95% CI 1.11-4.66) when more contaminated herbicides were used, but the number of cases was small (n=15). A within-group comparison found that in Comparison veterans, time served in SEA was associated with an increased risk of prostate cancer (RR=2.18, 95% CI 1.27-3.76, >789 days versus < or =789 days). No increase in the risk of prostate cancer was observed within the Ranch Hand group in association with TCDD or time served in SEA. These analyses suggest that a longer service in SEA and exposures other than TCDD may have increased the risk of prostate cancer in Comparison veterans.

Pahwa P, McDuffie HH, Dosman JA, McLaughlin JR, Spinelli JJ, Robson D, Fincham S. 2006 Mar. Hodgkin lymphoma, multiple myeloma, soft tissue sarcomas, insect repellents, and phenoxyherbicides. J Occup Environ Med 48(3):264-74.SEPAbstract: OBJECTIVE: The objective of this study was to determine if there is an additional risk of developing Hodgkin lymphoma, multiple myeloma, or soft tissue sarcoma as a consequence of exposure to a combination of phenoxyherbicides, rubber gloves, DEET (N, N-diethyl-m-toluamide), and sunlight compared with each of the individual chemicals. METHODS: This was a population-based study of men with specific cancers and age, province-matched control subjects. RESULTS: No additional risk from these combinations of exposures of developing these three types of tumor was found in contrast to non-Hodgkin lymphoma. CONCLUSIONS: The mechanisms by which phenoxyherbicides contribute to the risk of multiple myeloma and non-Hodgkin lymphoma may be different.

Kim HJ, Park YI, Dong MS. 2005 Nov. Effects of 2,4-D and DCP on the DHT-induced androgenic action in human prostate cancer cells . Toxicol Sci 88(1):52-9.SEPAbstract: 2,4-Dichlorophenoxyacetic acid (2,4-D) and its metabolite 2,4-dichlorophenol (DCP) are used extensively in agriculture as herbicides, and are suspected of potential endocrine disruptor activity. In a previous study, we showed that these compounds exhibited synergistic androgenic effects by co-treatment with testosterone in the Hershberger assay. To elucidate the mechanisms of the synergistic effects of these compounds on the androgenicity of testosterone, the androgenic action of 2,4-D and DCP was characterized using a mammalian detection system in prostate cancer cell lines. In in vitro assay systems, while 2,4-D or DCP alone did not show androgenic activity, 2,4-D or DCP with 5alpha-dihydroxytestosterone (DHT) exhibited synergistic androgenic activities. Co-treatment of 10 nM 2,4-D or DCP with 10 nM DHT was shown to stimulate the cell proliferation by 1.6-fold, compared to 10 nM DHT alone. In addition, in transient transfection assays, androgen-induced transactivation was also increased to a maximum of 32-fold or 1.28-fold by co-treatment of 2,4-D or DCP with DHT, respectively. However, 2,4-D and DCP exerted no effects on either mRNA or protein levels of

AR. In a competitive AR binding assay, 2,4-D and DCP inhibited androgen binding to AR, up to 50% at concentrations of approximately 0.5 microM for both compounds. The nuclear translocation of green fluorescent protein-AR fusion protein in the presence of DHT was promoted as the result of the addition of 2,4-D and DCP. Collectively, these results that 2,4-D and DCP enhanced DHT-induced AR transcriptional activity might be attributable, at least in part, to the promotion of AR nuclear translocation.

Mills PK, Yang R, Riordan D. 2005 Sep. Lymphohematopoietic cancers in the United Farm Workers of America (UFW), 1988-2001. Cancer Causes Control 16(7):823-30.Abstract: OBJECTIVE: Agricultural risk factors for lymphohematopoietic cancers (LHC) in Hispanic farm workers in California were examined in a nested case-control study embedded in a cohort of 139,000 ever members of a farm worker labor union in California. METHODS: Crop and pesticide exposures were estimated by linking county/month and crop specific job history information from union records with California Department of Pesticide Regulation pesticide use reports during the 20-year period prior to cancer diagnosis. RESULTS: A total of 131 LHC diagnosed in California between 1988 and 2001 were included in the analysis. Analyses were conducted by gender and subtype of non-Hodgkins lymphoma (nodal, extra nodal) and by leukemia histology (lymphocytic, granulocytic). Odds ratios were calculated by stratification and by unconditional logistic regression. Risk for all LHC was elevated in workers cultivating vegetables (OR = 1.67, 95% CI = 1.12-2.48). Risk of leukemia was associated with exposure to the pesticides mancozeb (OR = 2.35, 95% CI = 1.12-4.95) and toxaphene (OR = 2.20, 95% CI = 1.04-4.65) while **NHL risk was increased in association with 2,4-D (OR = 3.80, 95% CI=1.85-7.81)**. Risk of leukemia was particularly elevated among female workers and for granulocytic versus lymphocytic leukemia for several chemicals. No associations were noted for multiple myeloma. CONCLUSIONS: California farm workers employed where mancozeb and toxaphene were used had an increased risk of leukemia compared to farm workers employed elsewhere. Employment in farms using 2,4-D was associated with an increased risk of NHL.

McDuffie HH, Pahwa P, Robson D, Dosman JA, Fincham S, Spinelli JJ, McLaughlin JR. 2005 Aug. Insect repellents, phenoxyherbicide exposure, and non-Hodgkin's lymphoma. J Occup Environ Med 47(8):806-16.Abstract: OBJECTIVE: We sought to test a hypothetical explanation of contradictory results in studies of phenoxyherbicides and NHL, that the exposure of rubber gloves recommended for use by farmers when mixing or applying pesticides simultaneously to 2,4-D (2,4-dichlorophenoxyacetic acid), DEET (N,N-diethyl-m-toluamide), and ultraviolet rays increased their permeability to 2,4-D. METHODS: We conducted a case (NHL n = 513)/control (n = 1506) study among men using age; province of residence; exposure to insect repellents containing DEET, phenoxy-herbicides, or dicamba; and gloves when handling pesticides. RESULTS: Using conditional logistic regression, the stratum with reported exposure to mecoprop, to DEET and the use of rubber gloves had higher odds ratios (3.86; 95% confidence interval = 1.57-9.49) compared with strata with other combinations. CONCLUSIONS: In conclusion, the etiologic complexity of NHL was demonstrated.

Bharadwaj L, Dhami K, Schneberger D, Stevens M, Renaud C, Ali A. 2005 Aug. Altered gene expression in human hepatoma HepG2 cells exposed to low-level 2,4-dichlorophenoxyacetic acid and potassium nitrate. Toxicol In Vitro 19(5):603-19.Abstract: 2,4-dichlorophenoxyacetic acid (2,4-D) and nitrate are agricultural contaminants found in rural ground water. It is not known whether levels found in groundwater pose a human or environmental health risk, nor is the mechanism of toxicity at the molecular/cellular level understood. This study focused on determining whether 2,4-D or nitrate at environmentally realistic levels elicit gene expression changes in exposed cells. cDNA microarray technology was used to determine the impact of 2,4-D and nitrate in an in vitro model of exposure. Human hepatoma HepG2 cells were incubated with 2,4-D or nitrate alone for 24 h. Cell viability (neutral red assay) and proliferation (BrdU incorporation) were assessed following exposure. Total RNA from treated and control cells were isolated, reverse transcribed and reciprocal labelled with Cy3 or Cy5 dyes, and hybridized to a human cDNA microarray. The hybridized microarray chips were scanned, quantified and analyzed to identify genes affected by 2,4-D or nitrate exposure based on a two-fold increase or decrease in gene expression and reproducibility (affected in three or more treatments). Following filtering, normalization and hierarchical clustering initial data indicate that numerous genes were found to be commonly expressed in at least three or more treatments of 2,4-D or nitrate tested. The affected genes indicate that HepG2 cells respond to environmental, low-level exposure and produce a cellular response that is associated with alterations in the expression of many genes. The affected genes were characterized as stress response, cell cycle control,

immunological and DNA repair genes. These findings serve to highlight new pathway(s) in which to further probe the effects of environmental levels of 2,4-D and nitrate.

Mills PK, Yang R. 2005 Apr-Jun. Breast cancer risk in Hispanic agricultural workers in California. Int J Occup Environ Health 11(2):123-31. Abstract: In a registry-based case-control study of breast cancer in farm labor union members in California, 128 breast cancer (BC) cases newly diagnosed in 1988--2001 and 640 cancer-free controls were investigated. Stage and grade of disease at diagnosis were about the same as in the California Hispanic population. Risk of breast cancer was not associated with work with any specific crops or commodities except mushrooms, where the adjusted odds ratio (OR) was 6.00 (95% CI 2.01-18.0). Controlling for covariates, adjusted ORs (and 95% CIs) for breast cancer in quartiles of pesticide use were 1.00, 1.30 (0.73-2.30), 1.23 (0.67-2.27), and 1.41 (0.66-3.02). Chlordane, malathion, and 2,4-D were associated with increased risk. Risk associated with chemical use was stronger in younger women, those with early-onset breast cancer, and those diagnosed earlier (1988--1994).

Kern PA, Said S, Jackson WG Jr, Michalek JE. 2004 Sep. Insulin sensitivity following agent orange exposure in Vietnam veterans with high blood levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin. J Clin Endocrinol Metab 89(9):4665-72. Abstract: Our objective was to determine whether insulin sensitivity was related to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in Vietnam veterans exposed to Agent Orange. Air Force veterans of Operation Ranch Hand, the unit responsible for spraying Agent Orange and other herbicides in Vietnam from 1962 to 1971, and comparison veterans who did not spray herbicides were included. We measured insulin sensitivity (S(I)) using a frequently sampled iv glucose tolerance test in a matched study of 29 matched pairs of veterans and a quantitative insulin sensitivity check index (QUICKI) based on fasting glucose and insulin in 71 matched pairs. No group differences were found with regard to the mean values of S(I), QUICKI, TNFalpha, adiponectin, and two measures of insulin secretion. However, S(I) and QUICKI decreased significantly with regard to TCDD (P = 0.01 and 0.02). A corresponding pattern (although not significant) was found for blood levels of TNFalpha and adiponectin. These data suggest that high blood TCDD levels may promote an insulin-resistant state, but the magnitude of this effect appeared to be small, such that an 18-fold increase in blood TCDD due to increased exposure resulted in only a 10% change in S(I) in the 29 matched pairs.

Tuschl H, Schwab CE. 2004 Aug. Flow cytometric methods used as screening tests for basal toxicity of chemicals. Toxicol In Vitro 18(4):483-91. Abstract: Aim of the present study was to evaluate the suitability of flow cytometry to test in vitro effects of toxicants. Flow cytometry offers the possibility to study several parameters simultaneously, e.g. cell cycle modulation, apoptosis and necrosis within the same cell culture. The effects of six compounds (acetaminophen=AAP, isoniazid=INH, digoxin, malathion, paraquat and 2,4-dichlorophenoxy acetic acid=2,4-D) on cell cycle were investigated in HepG2 cells and the induction of apoptosis/necrosis was analyzed by a spectrum of flow cytometric assays in HepG2, AAH-1 and YAC-1 cells. Early indicators of apoptosis--loss of mitochondrial membrane polarization--as well as later events of the apoptotic process--annexin V binding and DNA fragmentation--were studied. The phases of the cell cycle and the occurrence of a sub-G(0) peak of apoptotic cells were determined with propidium iodide staining. The present investigation demonstrated good correlations between results obtained by flow cytometric analyses and the IC50 data of the MEIC (=Multicenter Evaluation of In Vitro Cytotoxicity) study. Regarding the short time required for the tests, the possibility of investigating several parameters of cytotoxicity simultaneously and the ease of performance, flow cytometric analyses are well suited for the pre-screening for toxic effects of chemicals.

Hong CC, Shimomura-Shimizu M, Muroi M, Tanamoto K. 2004 Jul. Effect of endocrine disrupting chemicals on lipopolysaccharide-induced tumor necrosis factor-alpha and nitric oxide production by mouse macrophages. Biol Pharm Bull 27(7):1136-9. Abstract: Little is known about the development of infectious diseases during exposure to endocrine disrupting chemicals (EDCs), although several studies have reported on the effect of EDCs on the immune function of the human body. To assess the effect of EDCs on the development of infectious disease, we investigated the effect of eighteen possible EDCs on mouse macrophage production of tumor necrosis factor-alpha (TNF-alpha) and nitric oxide (NO) in response to bacterial endotoxin in vitro and ex vivo. Of chemicals we examined, simazine, nitrofen, and benzyl butyl phthalate inhibited lipopolysaccharide (LPS)-induced TNF-alpha production by mouse macrophage cell line RAW 264 in vitro. Carbaryl, alachlor, nonylphenol, octylphenol, tributyltin, and

triphenyltin inhibited LPS-induced NO production in vitro, whereas 2,4-dichlorophenoxy acetic acid and bisphenol A enhanced its production. Zineb and alachlor, on the other hand, enhanced LPS-induced TNF-alpha production by mouse peritoneal macrophages ex vivo, while alachlor inhibited LPS/interferon-gamma-induced NO production ex vivo. These results indicate that some EDCs exert modulatory activity on endotoxin-induced macrophage activation either positively or negatively, suggesting that these compounds may affect the development of infectious diseases. This is the first report that systematically compared the effect of EDCs on LPS action.

Andra J, Koch MH, Bartels R, Brandenburg K. 2004 May. Biophysical characterization of endotoxin inactivation by NK-2, an antimicrobial peptide derived from mammalian NK-lysin. Antimicrob Agents Chemother 48(5):1593-9.[1]Abstract: NK-2, a membrane-acting antimicrobial peptide, was derived from the cationic core region of porcine NK-lysin and consists of 27 amino acid residues. It adopts an amphipathic, alpha-helical secondary structure and has been shown to interact specifically with membranes of negatively charged lipids. We therefore investigated the interaction of NK-2 with lipopolysaccharide (LPS), the main, highly anionic component of the outer leaflet of the outer membrane of gram-negative bacteria, by means of biophysical and biological assays. As model organisms and a source of LPS, we used Salmonella enterica strains with various lengths of the LPS carbohydrate moiety, including smooth LPS, rough LPS, and deep rough LPS (LPS Re) mutant strains. NK-2 binds to LPS Re with a high affinity and induces a change in the endotoxin-lipid A aggregate structure from a cubic or unilamellar structure to a multilamellar one. This structural change, in concert with a significant overcompensation of the negative charges of LPS, is thought to result in the neutralization of the endotoxic LPS activity in a cell culture system. Neutralization of LPS activity by NK-2 as well as its antibacterial activity against the various Salmonella strains strongly depends on the length of the sugar chains of LPS, with LPS Re being the most sensitive. This suggests that a hydrophobic peptide-LPS interaction is necessary for efficient neutralization of the biological activity of LPS and that the long carbohydrate chains, besides their function as a barrier for hydrophobic drugs, also serve as a trap for polycationic substances.

Giri VN, Cassidy AE, Beebe-Dimmer J, Ellis LR, Smith DC, Bock CH, Cooney KA. 2004 Apr. Association between Agent Orange and prostate cancer: a pilot case-control study. Urology 63(4):757-60; discussion 760-1.[1]Abstract: OBJECTIVES: To estimate in a pilot study the risk of being diagnosed with prostate cancer after exposure to Agent Orange in a clinical population of military veterans. Prostate cancer is the most common cancer diagnosed in American men and the second leading cause of cancer deaths. An association between Agent Orange and prostate cancer has been suggested by epidemiologic studies. METHODS: A case-control study was conducted at the Department of Veterans Affairs Medical Center in Ann Arbor, Michigan. Cases of pathologically diagnosed prostate cancer were identified and age matched in a 1:3 ratio with controls. Exposure to Agent Orange was assessed by reviewing the administrative portion of the computerized medical records. A subanalysis of the cases was conducted to examine the clinical features of prostate cancer in men reporting exposure to Agent Orange versus those who did not report exposure. RESULTS: A total of 47 military veterans with prostate cancer and 142 control men without prostate cancer were selected. After adjusting for age and race, men with prostate cancer were approximately two times more likely to report previous exposure to Agent Orange (odds ratio 2.06; 95% confidence interval 0.81 to 5.23). CONCLUSIONS: The results from this pilot study suggest exposure to Agent Orange is associated with an increased risk of prostate cancer. Additional study in larger populations is necessary to confirm and to quantify this association more accurately.

Ambrus JL, Islam A, Akhter S, Dembinski W, Kulaylat M, Ambrus CM. 2004. Multiple medical problems following agent orange exposure. J Med 35(1-6):265-9.[1]Abstract: A patient exposed to agent orange and a gunshot wound during the Vietnam War has developed multiple medical problems including nocardiosis, onychomycosis (Trichophyton rubrum), multiple thromboembolic episodes, hemochromatosis, diabetes mellitus type 2, diabetic neuropathy, activated protein C resistance (without Leyden V 1st mutation), degree A-V block, lung cancer (metastatic adenocarcinoma), carpal tunnel syndrome and arthritis.

Chaudhuri A, Harris MD. 2003 Nov. 'Proximal-type' epithelioid sarcoma: is Agent Orange still at large? Ann R Coll Surg Engl 85(6):410-2.[1]Abstract: BACKGROUND AND AIMS: Proximal-type epithelioid sarcomas of the perineum are extremely rare. The authors provide an overview of this condition in relation to the history of exposure to Agent Orange. PATIENT AND METHODS: A 54-year-old man presented with a rapidly

growing perineal subcutaneous mass that was shown to be a proximal-type epithelioid sarcoma. The case is discussed. An Internet Medline search was performed and the current literature reviewed. RESULTS: Only 4 primary perineal sarcomas have been described in the literature. Epithelioid sarcomas are uncommon, aggressive tumours with a propensity for locoregional recurrence. They are recognised by the US Veterans Affairs department as linked to exposure to Agent Orange, an organochlorine defoliant containing the contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). However, the role of Agent Orange in sarcomagenesis is still controversial. CONCLUSION: Unusual soft tissue swellings in a background of chemical exposure should be investigated thoroughly with a view to early, appropriate treatment.

Frumkin H. 2003 Jul-2003 Aug 31. Agent Orange and cancer: an overview for clinicians. CA Cancer J Clin 53(4):245-55.

Kim HA, Kim EM, Park YC, Yu JY, Hong SK, Jeon SH, Park KL, Hur SJ, Heo Y. 2003 Jul. Immunotoxicological effects of Agent Orange exposure to the Vietnam War Korean veterans. Ind Health 41(3):158-66 .Abstract: Immunomodulatory effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) demonstrated using animals are thymic atrophy, downregulation of cytotoxic T or B lymphocyte differentiation or activation, whereas human immunotoxicities have not been investigated well. This study was undertaken to evaluate overall immunologic spectrum of the Vietnam War Korean veterans exposed to Agent Orange contaminated with TCDD. Quantity of red blood cells, hemoglobin and hematocrit in the veterans suffered from chronic diseases associated with Agent Orange exposure (Veterans-patient group) were decreased in comparison with those of the veterans without the diseases and the age-matched healthy controls, but no differences in leukocyte populations. Plasma IgG levels were lowered in the veterans than the controls, owing to significant decrease in the IgG1 levels. Increase in the IgE levels was observed in the plasma from the veterans. Alteration of T cell-mediated immunity was also resulted from activation of peripheral blood mononuclear cells with polyclonal T cell activators. Production of IFNgamma, a major cytokine mediating host resistance against infection or tumoregenesis, was lowered in the veterans-patient group. However, production of IL-4 and IL-10, representative cytokines involved with hypersensitivity induction, was enhanced in the patient group. Overall, this study suggests that military service in Vietnam and/or Agent Orange exposure disturbs immune-homeostasis resulting in dysregulation of B and T cell activities.

Beaulieu A, Fessele K. 2003 May-Jun. Agent Orange: management of patients exposed in Vietnam. Clin J Oncol Nurs 7(3):320-3.Abstract: Since the Vietnam War ended in 1975, numerous studies have been conducted to determine if an association exists between Agent Orange exposure and certain disabling conditions specifically cancer. Although a definite causal relationship has not yet been established, sufficient data associate Agent Orange with certain conditions. Because of their advancing age similar to other baby boomers, Vietnam veterans are at a higher risk of developing malignancies. However, their exposure to Agent Orange also may increase their risk for cancer and other associated diseases. This article examines the latest findings of scientific research sponsored by the Department of Veterans Affairs and discusses the importance of well-informed oncology nurses when providing care for patients with cancer exposed to Agent Orange.

Tuschl H, Schwab C. 2003 Mar. Cytotoxic effects of the herbicide 2,4-dichlorophenoxyacetic acid in HepG2 cells. Food Chem Toxicol 41(3):385-93.Abstract: 2,4-Dichlorophenoxyacetic acid (2,4-D) and its derivatives are herbicides widely used to control the growth of broadleaf and woody plants. Although 2,4-D is well known to be moderately toxic, little information is available on the mechanisms of its toxicity. Results on carcinogenicity, genotoxicity and mutagenicity are contradictory, but neurotoxic, immunosuppressive and hepatotoxic effects have been defined. The aim of the present study was to investigate the cytotoxic effects of 2,4-D on a human hepatoma cell line. HepG2 cells were treated with different concentrations of 2,4-D, and cell viability, induction of apoptosis/necrosis and cell cycle phases were determined. Apoptosis was detected in flow cytometric light scatter histograms, the annexin V assay, the determination of DNA strand breaks with the TUNEL assay and the occurrence of a sub G(0) peak after propidium iodide (PI) staining. The induction of apoptosis by 2,4-D was accompanied by a disruption of the mitochondrial membrane potential as verified by staining with the cationic JC-1 probe. In addition, 2,4-D affected the cell cycle in a concentration-dependent manner. Our investigation suggested that 2,4-D exerts its cytotoxic effects by the induction of apoptosis via a direct effect on the mitochondrial membrane potential.

Knapp GW, Setzer RW, Fuscoe JC. 2003. Quantitation of aberrant interlocus T-cell receptor rearrangements in mouse thymocytes and the effect of the herbicide 2,4-dichlorophenoxyacetic acid. Environ Mol Mutagen 42(1):37-43.Abstract: Small studies in human populations have suggested a correlation between the frequency of errors in antigen receptor gene assembly and lymphoid malignancy risk. In particular, agricultural workers exposed to pesticides have both an increased risk for lymphoma and an increased frequency of errors in antigen receptor gene assembly. In order to further investigate the potential of such errors to serve as a mechanistically based biomarker of lymphoid cancer risk, we have developed a sensitive PCR assay for quantifying errors of V(D)J recombination in the thymocytes of mice. This assay measures interlocus rearrangements between two T-cell receptor loci, V-gamma and J-beta, located on chromosomes 13 and 6, respectively. The baseline frequency in four strains of mice was determined at several ages (2-8 weeks of age) and was found to be stable at approximately 1.5 x 10(-5) per thymocyte. Strain AKR, which has a high susceptibility to T-cell lymphomas, did not show an elevated frequency of aberrant V(D)J events. We used this assay to examine the effects of the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) on the frequency of these events. Female B6C3F1 mice, 27 days of age, were exposed to 2,4-D by gavage at doses of 0, 3, 10, 30, and 100 mg/kg/day for 4 successive days and sacrificed on day 5. Thymus DNA was isolated and examined for illegitimate V(D)J recombination-mediated gene rearrangements. In addition, pregnant mice were exposed to 2,4-D and thymocytes from the offspring examined at 2 weeks of age. No significant increase in aberrant V(D)J rearrangements was found, indicating that under these conditions 2,4-D does not appear to effect this important mechanism of carcinogenesis.

Ahmad K. 2002 Apr. Agent Orange no longer linked to childhood AML. Lancet Oncol 3(4):199.

Meyer KM. 2002 Feb. Incidence of CTCL in Vietnam veterans. Dermatol Nurs 14(1):42, 45, 52.Abstract: The causative factors of cutaneous T-cell lymphoma (CTCL) are unclear. Exposure to herbicides has been linked to the development of other lymphomas. Three Vietnam Veterans with CTCL treated at a photopheresis unit in New Jersey report positive histories of exposure to Agent Orange, a herbicide used during the war.

McDuffie HH, Pahwa P, McLaughlin JR, Spinelli JJ, Fincham S, Dosman JA, Robson D, Skinnider LF, Choi NW. 2001 Nov. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. Cancer Epidemiol Biomarkers Prev 10(11):1155-63 .Abstract: Our objective in the study was to investigate the putative associations of specific pesticides with non-Hodgkin's Lymphoma [NHL; International Classification of Diseases, version 9 (ICD-9) 200, 202]. We conducted a Canadian multicenter population-based incident, case (n = 517)-control (n = 1506) study among men in a diversity of occupations using an initial postal questionnaire followed by a telephone interview for those reporting pesticide exposure of 10 h/year or more, and a 15% random sample of the remainder. Adjusted odds ratios (ORs) were computed using conditional logistic regression stratified by the matching variables of age and province of residence, and subsequently adjusted for statistically significant medical variables (history of measles, mumps, cancer, allergy desensitization treatment, and a positive history of cancer in first-degree relatives). We found that among major chemical classes of herbicides, the risk of NHL was statistically significantly increased by exposure to phenoxyherbicides [OR, 1.38; 95% confidence interval (CI), 1.06-1.81] and to dicamba (OR, 1.88; 95% CI, 1.32-2.68). Exposure to carbamate (OR, 1.92; 95% CI, 1.22-3.04) and to organophosphorus insecticides (OR, 1.73; 95% CI, 1.27-2.36), amide fungicides, and the fumigant carbon tetrachloride (OR, 2.42; 95% CI, 1.19-5.14) statistically significantly increased risk. Among individual compounds, in multivariate analyses, the risk of NHL was statistically significantly increased by exposure to the herbicides 2,4-dichlorophenoxyacetic acid (2,4-D; OR, 1.32; 95% CI, 1.01-1.73), mecoprop (OR, 2.33; 95% CI, 1.58-3.44), and dicamba (OR, 1.68; 95% CI, 1.00-2.81); to the insecticides malathion (OR, 1.83; 95% CI, 1.31-2.55), 1,1,1-trichloro-2,2-bis (4-chlorophenyl) ethane (DDT), carbaryl (OR, 2.11; 95% CI, 1.21-3.69), aldrin, and lindane; and to the fungicides captan and sulfur compounds. In additional multivariate models, which included exposure to other major chemical classes or individual pesticides, personal antecedent cancer, a history of cancer among first-degree relatives, and exposure to mixtures containing dicamba (OR, 1.96; 95% CI, 1.40-2.75) or to mecoprop (OR, 2.22; 95% CI, 1.49-3.29) and to aldrin (OR, 3.42; 95% CI, 1.18-9.95) were significant independent predictors of an increased risk for NHL, whereas a personal history of measles and of allergy desensitization treatments lowered the risk. We concluded that NHL was associated with specific pesticides after adjustment for other independent

predictors.

Zafar MB, Terris MK. 2001 Jul. Prostate cancer detection in veterans with a history of Agent Orange exposure. J Urol 166(1):100-3.Abstract: PURPOSE: Agent Orange, a chemical that was widely used in the Vietnam War as a defoliant, is widely accepted as a health hazard but its potential causative role in prostate cancer has been controversial. We evaluated the rate of prostate cancer in veterans referred for prostate biopsy who reported a history of Agent Orange exposure compared to the rate in veterans who denied such exposure. MATERIALS AND METHODS: A total of 400 consecutive veterans referred for prostate needle biopsy in a 30-month period completed a survey regarding Agent Orange exposure. Of these 400 patients 32 (8%) reported previous exposure to Agent Orange. From the remaining 368 patients who denied Agent Orange exposure 3 consecutive age matched controls were selected per each patient reporting exposure for a total of 96 age matched controls. Prostate specific antigen, prostate cancer, cancer grade and length of cancer in the biopsy cores were compared in Agent Orange exposed patients and unexposed controls. To determine whether the patient population referred for biopsy was skewed by proportionally more exposed and referred than unexposed patients those referred for biopsy were compared to the overall adult male veteran population followed at the outpatient clinics at our facility. RESULTS: Of the 32 Agent Orange exposed patients 13 (41%) had prostate cancer, while 33 of the 96 controls (34.4%) had cancer. There was no correlation of Agent Orange exposure with cancer ($r = 0.06$). There was also no statistically significant difference in the 2 groups in regard to PSA ($p = 0.90$), cancer ($p = 0.15$), proportion of well differentiated cancers ($p = 0.41$) or length of cancer in the biopsy cores ($p = 0.34$). Compared with the total adult male veteran population followed on an outpatient basis at our facility an average of 1.07% of those with a history of Agent Orange exposure were referred for prostate biopsy yearly versus 1.33% of unexposed patients. CONCLUSIONS: Agent Orange may have a role in the causation of some types of cancer but we identified no significant relationship of prostate cancer with Agent Orange exposure in patients referred for prostate biopsy.

Kaioumova D, Susal C, Opelz G. 2001 Jan. Induction of apoptosis in human lymphocytes by the herbicide 2,4-dichlorophenoxyacetic acid. Hum Immunol 62(1):64-74.Abstract: Dimethylammonium salt of 2,4-dichlorophenoxyacetic acid (DMA-2,4-D) is a widely used herbicide that is considered moderately toxic. In the present study we found that DMA-2,4-D is able to cause apoptosis in peripheral blood lymphocytes of healthy individuals and Jurkat T cells. Apoptosis induced by DMA-2,4-D was dose and time dependent, independent of Fas, TNF receptor 1 or the aromatic hydrocarbon receptor, and involved disruption of the mitochondrial transmembrane potential and activation of caspase-9. ZVAD-FMK, a broad-spectrum inhibitor of caspases, blocked DMA-2,4-D-induced apoptosis completely. While an inhibitor of caspase-9, as well as caspase-9 and caspase-3 inhibitors in combination, strongly blocked DMA-2,4-D-induced apoptosis, an inhibitor of caspase-3 had a moderate inhibitory effect. Unlike Fas-mediated apoptosis, the initiator caspase, caspase-8, was not involved in DMA-2,4-D-induced apoptosis. Transfection of Jurkat cells with Bcl-2 prevented DMA-2,4-D-induced disruption of the mitochondrial transmembrane potential and led to a complete blockage of apoptosis. Our data indicate that DMA-2,4-D kills human lymphocytes by initiating apoptosis via a direct effect on mitochondria. The activation of caspases occurs downstream of mitochondrial damage, and the dysfunction of mitochondria appears to be sufficient for triggering all downstream events leading to apoptosis.

Goldsmith DF. 2000. Linking environmental cancer with occupational epidemiology research: the role of the International Agency for Research on Cancer (IARC). J Environ Pathol Toxicol Oncol 19(1-2):171-5.Abstract: BACKGROUND: The International Agency for Research on Cancer (IARC) provides the most credible assessment of carcinogenicity for the scientific community. IARC Monographs also suggest areas where new laboratory and epidemiology research on cancer should be focused. REVIEW: This presentation examines two recent IARC reports on silica and coal dust (from 1997), and on occupational exposures to insecticide and pesticide applications (from 1991). RESULTS: From the Silica Monograph, the research implications suggest that laboratory and epidemiology studies would be useful focusing on mixtures of hazards where silica is a significant component of the respirable environment: in coal mining (which has an excess of gastric cancers) with variations in silica exposure; in uranium mining where there is silica dust plus radon decay products, in foundries and steel-making plants where silica exposure is common as are other carcinogenic hazards; in agriculture where dusty farming may be common, and comparisons are needed with other polymorphs of silica, including amorphous quartz. Additional studies of

lymphatic, dermal, and gastrointestinal malignancies are needed to determine if the evidence of silicocarcinogenesis extends to these tumor sites. Finally, some fundamental studies of adsorptive capability of silica and resultant biologic activity, including biomarker studies, are needed. In the pesticide realm, there are many active ingredients that have been shown to be 2B (or possible) carcinogens based on animal studies (or other evidence). Industrial epidemiology studies of workers manufacturing or handling chemicals such as atrazine, chlordane, dichlorvos, 2,4-D, and DDT should be undertaken. Cancer epidemiology associations have been demonstrated for chemicals such as phenoxy acid herbicides, 2,4,5-T, lindane, methoxychlor, toxaphene, and several organophosphate insecticides for which laboratory studies are needed. CONCLUSIONS: IARC reviews offer many leads for future research and insightful protocols that can provide new leads for studying these common exposures under novel environmental conditions.

Rosenberg AM, Semchuk KM, McDuffie HH, Ledingham DL, Cordeiro DM, Cessna AJ, Irvine DG, Senthilselvan A, Dosman JA. 1999 Jun 25. Prevalence of antinuclear antibodies in a rural population. J Toxicol Environ Health A 57(4):225-36.[1]Abstract: Exposure to environmentally and occupationally encountered toxicants can be associated with the development of certain autoimmune diseases and with the induction of antinuclear antibodies (ANA). Some chemicals used in the agricultural industry are known to affect immune function but their roles in the induction of autoimmunity in general, and ANA in particular, have not been reported previously. This study was undertaken to establish the prevalence of ANA in a rural population and to determine environmental and occupational exposures with which they are associated. This cross-sectional study represented one component of an interdisciplinary project (Prairie Ecosystem Study [PECOS], Eco-Research Program, Tri-Council Secretariat of Canada) designed to explore, in a rural population, the roles of environmental exposures as determinants of human health status. Information regarding lifetime, current, and main occupational exposures in the rural-dwelling study population was derived from a self-administered questionnaire. Sera from consenting subjects, collected during the months of February and March 1996, were assayed for ANA by indirect immunofluorescence on HEp-2 cells. The study population comprised 322 adult subjects (mean age 49.3+/-14.7 yr; range 16-87 yr). Statistical analyses adjusted for age and sex revealed that the presence of ANA among the participants was associated with a current agricultural occupation that included oilseed production, hog production, or poultry production. There was a significant association between ANA positivity and a current main farming operation of crop production. There was also an association among individual participants between lifetime exposure to the insecticide class of pesticides and the presence of ANA. In this rural study population, ANA positivity was significantly associated with lifetime exposure specifically to carbamate, organochlorine (including aldrin, chlordane, dieldrin, endrin, heptachlor, and lindane, but excluding DDT and methoxychlor), and pyrethroid insecticides and to phenoxyacetic acid herbicides, including 2,4-D. After adjustment for age, sex, and other insecticide exposures, multivariate analyses indicated that ANA positivity was associated with current oilseed production and with lifetime exposure to pyrethroid insecticides. In a rural population, ANA were associated with production of certain crops and certain animals and exposure to specific pesticides. The data indicate that some occupational exposures related to the agricultural industry are associated with the presence of ANA, a serologic expression of autoimmunity.

Watanabe S, Kitamura K, Nagahashi M. 1999 Feb. Effects of dioxins on human health: a review. J Epidemiol 9(1):1-13.[1]Abstract: The toxicity of 2,3,7,8-tetrachlorodibenzodioxin (TCDD) has been known since 1950s. TCDD is a by-product of herbicide 2,4-dichloroacetophenol (2,4-D) and 2,4,5-trichloroacetophenol (2,4,5-T), but it was first found in fryash of municipal incinerator in 1979 in Japan. In 1998, the survey of municipal incinerators revealed that 105 out of 1,641 produced above the allowed emission level of 80 ng TEQ/m3. Total annual release of dioxins is estimated to be about 5,000 g TEQ in 1997 in Japan. Japanese government started a comprehensive survey for dioxin levels in milk and blood of residents around incinerators, and their health effects. Human effects by dioxin exposures in Western countries were mostly acute and at high level in accidentally and/or occupationally. Health effects of low-dose and long lasting exposure has not been well understood. Certain amount of polychlorinated dibenzo-p-dioxins (PCDD), dibenzofurans (PCDF) and polychlorinated biphenyls (PCB) is accumulated in our body. Mother's milk is also contaminated by PCDD/PCDF. Health effects of the polychlorinated chemicals are summarized, and the necessity of regulations and recommendations for making a guideline is discussed in this review.

Fontana A, Picoco C, Masala G, Prastaro C, Vineis P. 1998 Nov-Dec. Incidence rates of lymphomas and environmental measurements of phenoxy herbicides: ecological analysis and case-control study. Arch

Environ Health 53(6):384-7.[1]Abstract: The authors conducted an ecological study of the distribution of malignant lymphomas in a rice-growing area in northern Italy. They considered data on concentrations of phenoxy herbicides in soil and water and found the highest incidence of non-Hodgkin's lymphoma in subjects who lived in an area where 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid existed in very high concentrations. During 1985-1988, the incidence of non-Hodgkin's lymphoma in males in the most-polluted municipalities was twice as high as was noted for the remaining less-polluted territories. During 1991-1993, non-Hodgkin's lymphoma was higher by 60%. The authors also conducted a population-based case-control study. They found an association between employment of women in rice-growing jobs (particularly as rice weeders) and risk of non-Hodgkin's lymphoma (odds ratio=1.9; 95% confidence interval=0.6, 6.0). Work in rice fields was correlated strongly with residence in polluted areas. The authors did not detect an association between area of residence or occupation and incidence of Hodgkin's disease.

Blair A, Cantor KP, Zahm SH. 1998 Jan. Non-hodgkin's lymphoma and agricultural use of the insecticide lindane. Am J Ind Med 33(1):82-7.[1]Abstract: Data from population-based case-control studies of non-Hodgkin's lymphoma among white men from Kansas, Nebraska, Iowa, and Minnesota were pooled to evaluate potential risks from environmental exposures in more detail, while controlling for potential confounding factors. These data provided the opportunity to evaluate the risk of non-Hodgkin's lymphoma from potential exposures to lindane, a pesticide that causes cancer in laboratory animals and has been associated with human cancer in a few epidemiologic investigations. This pooled data set includes 987 individuals with non-Hodgkin's lymphoma and 2,895 population-based controls. Information was obtained by telephone or in person interviews, which included detailed questions on farm practices and agricultural use of chemicals. Logistic regression was used to calculate odds ratios (ORs) adjusted for age, state of residence, and subject or proxy interviews. Reported use of lindane significantly increased the risk of non-Hodgkin's's lymphoma by 50%. Some use characteristics were suggestive of an association. ORs were greater among persons who first used the pesticide 20 years before diagnosis (OR = 1.7) than more recently (OR = 1.3), among those who reported more frequent use (OR = 2.0 for use 5 or more days per year versus 1.6 for fewer than five days per year), and from use on crops (OR = 1.9), rather than from use on animals (OR = 1.3), although these differences were not statistically significant. On the other hand, ORs were lower when based on direct interviews (OR = 1.3) than on data from proxy respondents (OR = 2.1) and adjustment for potential confounding by use of 2,4-D and diazinon reduced the ORs associated with lindane use from 1.5 to 1.2 and 1.3, respectively. Lindane does not appear to be a major etiologic factor in the development of non-Hodgkin's's lymphoma, although a small role cannot be ruled out.

Hardell L, Eriksson M, Axelson O. 1998. Agent Orange in war medicine: an aftermath myth. Int J Health Serv 28(4):715-24.[1]Abstract: Since the late 1970s several epidemiological studies have appeared linking exposure to phenoxy herbicides or chlorophenols to some malignant tumors. Most of these compounds are contaminated with dioxins and dibenzofurans; for example, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is a contaminant of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), a component of Agent Orange which was sprayed in Vietnam during the war. The results of some of the epidemiological studies on cancer risks associated with exposure to these compounds have been manipulated and misinterpreted, particularly by the Australian Royal Commission on the Use and Effects of Chemical Agents on Australian Personnel in Vietnam. Furthermore, a book on Australian war history entitled Medicine at War, commissioned by the Federal Government, reiterates several of these misinterpretations, despite available contrary evaluations from Australian and U.S. authorities. These remarkable and confusing circumstances in the scientific process are considered also in the light of the recent classification of TCDD as carcinogenic to humans, Group 1, by a Working Group at the International Agency for Research on Cancer in Lyon, France.

Zahm SH. 1997 Nov. Mortality study of pesticide applicators and other employees of a lawn care service company. J Occup Environ Med 39(11):1055-67.[1]Abstract: In response to reports linking non-Hodgkin's lymphoma (NHL) and the herbicide 2,4-dichlorophenoxyacetic acid, a retrospective cohort mortality study of 32,600 employees of a lawn care company was conducted. The cohort was generally young with short-duration employment and follow-up. In comparison to the US population, the cohort had significantly decreased mortality from all causes of death combined (307 deaths), arteriosclerotic heart disease, and accidents. There were 45 cancer deaths (59.6 expected, standardized mortality ratio [SMR] = 0.76, 95% confidence interval [CI] = 0.55, 1.01). Bladder cancer mortality was significantly increased, but two of the three

observed deaths had no direct occupational contact with pesticides. There were four deaths due to NHL (SMR = 1.14, CI = 0.31, 2.91); three were male lawn applicators (SMR = 1.63, CI = 0.33, 4.77), with two of the applicators employed for three or more years (SMR = 7.11, CI = 1.78, 28.42). No other cause of death was significantly elevated among lawn applicators as a group or among those employed for three or more years. Although based on very small numbers and perhaps due to chance, the NHL excess is consistent with several earlier studies.

Mahan CM, Bullman TA, Kang HK, Selvin S. 1997 Aug. A case-control study of lung cancer among Vietnam veterans. J Occup Environ Med 39(8):740-7.SEPAbstract: Because of concerns among veterans over Agent Orange exposure, the Department of Veterans Affairs (VA) has conducted a series of studies of specific cancers among Vietnam veterans. Lung cancer is the topic of investigation in this report. The VA's Patient Treatment File (PTF) was used to identify 329 Vietnam era veterans with a diagnosis of lung cancer made between 1983 and 1990. The PTF is a computerized hospitalized database of inpatient records, including patients' demographic data, and diagnoses. A record is created for each patient discharged from any one of the VA's Medical Centers. Variables abstracted from the military record include education, race, branch of service, Military Occupational Specialty Code, rank, and units served within Vietnam. Two hundred sixty-nine controls were randomly selected from the PTF file of men hospitalized for a reason other than cancer. A second control group numbering 111 patients with colon cancer was also selected from the PTF file. Data were also gathered on exposure to Agent Orange through the location of each individual ground troop veteran's unit in relation to an area sprayed and the time elapsed since that area was sprayed. The crude odds ratio between service in Vietnam and lung cancer was of borderline significance (odds ratio = 1.39 with 95% confidence interval = 1.01-1.92). The relationship disappeared when the confounder year of birth was considered. We conclude from these data that there is no evidence of increased risk in lung cancer associated with service in Vietnam at this time.

Clapp RW. 1997 Jun. Update of cancer surveillance of veterans in Massachusetts, USA. Int J Epidemiol 26(3):679-81.

Pineau T, Hudgins WR, Liu L, Chen LC, Sher T, Gonzalez FJ, Samid D. 1996 Aug 23. Activation of a human peroxisome proliferator-activated receptor by the antitumor agent phenylacetate and its analogs. Biochem Pharmacol 52(4):659-67.SEPAbstract: The aromatic fatty acid phenylacetate and its analogs induce tumor cytostasis and differentiation in experimental models. Although the underlying mechanisms of action are not clear, effects on lipid metabolism are evident. We have now examined whether these compounds, structurally similar to the peroxisome proliferator clofibrate, affect the human peroxisome proliferator-activated receptor (hPPAR), a homolog of the rodent PPAR alpha, a transcriptional factor regulating lipid metabolism and cell growth. Gene transfer experiments showed activation of hPPAR, evident by the increased expression of the reporter gene chloramphenicol acetyltransferase linked to PPAR-response element from either the rat acyl-CoA oxidase or rabbit CYP4A6 genes. **The relative potency** of tested drugs in the co-transfection assay was: 4-iodophenylbutyrate > 4-chlorophenylbutyrate > clofibrate > phenylbutyrate > naphthylacetate > **2,4-D** > 4-chlorophenylacetate > phenylacetate >> indoleacetate. Phenylacetylglutamine, in which the carboxylic acid is blocked, was inactive. The ability of the aromatic fatty acids to activate PPAR was confirmed in vivo, as CYP4A mRNA levels increased in hepatocytes of treated rats. Further studies using human prostate carcinoma, melanoma, and glioblastoma cell lines showed a tight correlation between drug-induced cytostasis, increased expression of the endogenous hPPAR, and receptor activation documented in the gene-transfer model. These results identify phenylacetate and its analogs as a new class of aromatic fatty acids capable of activating hPPAR, and suggest that this nuclear receptor may mediate tumor cytostasis induced by these drugs.

Liu RC, Hahn C, Hurtt ME. 1996 Mar. The direct effect of hepatic peroxisome proliferators on rat Leydig cell function in vitro. Fundam Appl Toxicol 30(1):102-8.SEPAbstract: A review of the literature indicates that some compounds which produce hepatic peroxisome proliferation in rats also appear to produce Leydig cell adenomas, and some also affect the serum concentrations of testosterone and estradiol. Previous studies with the peroxisome proliferator ammonium perfluorooctanoate showed a direct effect on Leydig cells to alter steroidogenesis. It was therefore proposed that peroxisome proliferators in general may directly affect Leydig cell function to produce Leydig cell tumors by some undetermined mechanism. The present study investigated whether the following peroxisome proliferators directly affect Leydig cell function in vitro:

2,4-dichlorophenoxyacetic acid, ammonium perfluorooctanoate, acetylsalicylic acid, clofibric acid, ciprofibrate, gemfibrozil, tiadenol, tibric acid, trichloroacetic acid, trichloroethylene, and Wyeth 14,643. Leydig cells, isolated from adult Crl:CDBR rats (12-16 weeks old), were treated with peroxisome proliferator for 21 hr and the medium was assayed for estradiol. The function of the treated Leydig cell was evaluated by measuring the release of testosterone in response to human chorionic gonadotropin (hCG). In general, the peroxisome proliferators reduced the hCG-stimulated release of testosterone and either reduced or had no effect on the baseline release of testosterone. Of the 11 peroxisome proliferators, 8 increased the release of estradiol from Leydig cells treated for 1 day. Two more compounds were found to increase estradiol production when the treatment period was extended to 2 days. These effects were seen at noncytotoxic doses and at concentrations similar to those achieved in rat serum in dietary studies. The results suggest that peroxisome proliferators, as a class of compounds, directly modify the steroidogenic function of Leydig cells in vitro. Some of these compounds are known to produce Leydig cell tumors in rats, but this association has yet to be established for other peroxisome proliferators. This suggests that compounds which directly affect Leydig cell function in vitro may also induce Leydig cell tumors in vivo. Further investigations are necessary to address the mechanism for the in vitro effects on Leydig cells and to clarify the apparent relationship between peroxisome proliferator-induced changes in Leydig cell function and the development of Leydig cell tumors.

Dalager NA, Kang HK, Burt VL, Weatherbee L. 1995 Sep. Hodgkin's disease and Vietnam service. Ann Epidemiol 5(5):400-6. Abstract: Earlier studies that showed an association between exposure to phenoxy herbicides and the risk of malignant lymphomas have sparked concerns among Vietnam veterans over Agent Orange exposure. The Department of Veterans Affairs (VA) undertook a hospital-based case-control study to examine the association between military service in Vietnam and several histologic types of malignant lymphomas. This is a report of 283 Vietnam-era veteran patients who were treated in one of 172 VA hospitals from 1969 to 1985 with a diagnosis of Hodgkin's Disease (HD). Four hundred and four Vietnam-era veteran patients with diagnosis other than malignant lymphoma served as a comparison group. Military service in Vietnam was not associated with any significant increase in the risk of HD (adjusted odds ratio = 1.28; 95% confidence interval = 0.94, 1.76). Surrogate measures of potential Agent Orange exposure such as service in a specific military branch, in a certain region within Vietnam, in a combat role, or extended Vietnam service time were not associated with any significant increased risk of HD.

Kogevinas M, Kauppinen T, Winkelmann R, Becher H, Bertazzi PA, Bueno-de-Mesquita HB, Coggon D, Green L, Johnson E, Littorin M, et al. 1995 Jul. Soft tissue sarcoma and non-Hodgkin's lymphoma in workers exposed to phenoxy herbicides, chlorophenols, and dioxins: two nested case-control studies. Epidemiology 6(4):396-402. Abstract: We examined the effect of exposure to chemicals present in the production and spraying of phenoxy herbicides or chlorophenols in two nested case-control studies of soft tissue sarcoma and non-Hodgkin's lymphoma. Eleven sarcoma and 32 lymphoma cases occurring within an international cohort were matched for age, sex, and country of residence with 55 and 158 controls, respectively. Exposures to 21 chemicals or mixtures were estimated by three industrial hygienists who were blind to the subject's case-control status. Excess risk of soft tissue sarcoma was associated with exposure to any phenoxy herbicide [odds ratio (OR) = 10.3; 95% confidence interval (CI) = 1.2-91] and to each of the three major classes of phenoxy herbicides (2,4-dichlorophenoxyacetic acid, 2,4,5-trichlorophenoxyacetic acid, and 4-chloro-2-methylphenoxyacetic acid), to any polychlorinated dibenzodioxin or furan (OR = 5.6; 95% CI = 1.1-28), and to 2,3,7,8-tetrachlorodibenzo-p-dioxin (OR = 5.2; 95% CI = 0.85-32). Sarcoma risk was not associated with exposure to raw materials or other process chemicals. In the non-Hodgkin's lymphoma study, associations were generally weaker than those found in the study on sarcoma. These findings indicate that workers exposed to phenoxy herbicides and their contaminants are at a higher risk of soft tissue sarcoma.

Pierce S. 1995 Jun. The purported link between agent orange and cancer. Hum Pathol 26(6):693-5.

Dwyer JH, Flesch-Janys D. 1995 Apr. Agent Orange in Vietnam. Am J Public Health 85(4): 476-8.

[Anonymous]. 1995 Mar. Agent Orange down under . Environ Health Perspect 103(3):222.

Blair A, Hoar Zahm S. 1995 Feb. Overinterpretation of small numbers in the Dow 2,4-D cohort study. J Occup

Environ Med 37(2):126-7.

Asp S, Riihimaki V, Hernberg S, Pukkala E. 1994 Aug. Mortality and cancer morbidity of Finnish chlorophenoxy herbicide applicators: an 18-year prospective follow-up. Am J Ind Med 26(2):243-53.[1]Abstract: An 18-year follow-up for mortality and cancer morbidity was conducted in a cohort of 1,909 men who had started spraying chlorophenoxy herbicides (mixture of 2,4-dichlorophenoxyacetic acid [2,4-D] and 2,4,5-trichlorophenoxyacetic acid [2,4,5-T]) in 1955 through 1971. In all, 384 persons had died during the follow-up, and there was a slight deficit in natural deaths (standardized mortality ratio [SMR] 0.84; 95% confidence interval [CI] 0.75-0.94). By contrast, there was a small, nonsignificant increase in accidental and violent deaths. The overall cancer mortality was slightly less than in the general population (SMR 0.83; 95% CI 0.65-1.02), and not a single case of death of non-Hodgkin's lymphomas (NHL) or soft tissue sarcomas (STS) was detected. With regard to cancer morbidity, the incident cases showed a slight deficit compared to the population figure (standardized incidence ratio [SIR] 0.81; 95% CI 0.67-0.97). One case of NHL was found (2.4 expected with 10 years of latency), but not a single case of STS (0.8 expected with 10 years of latency). While our study does not support the contention that spraying of 2,4-D and 2,4,5-T containing herbicides carries any significant risk of cancer, the medium to low statistical power of the study does not allow any far reaching negative conclusions regarding the carcinogenicity of the agents.

Hardell L, Eriksson M, Degerman A. 1994 May 1. Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage, and anatomical localization of non-Hodgkin's lymphoma. Cancer Res 54(9):2386-9.[1]Abstract: Results on 105 cases with histopathologically confirmed non-Hodgkin's lymphoma (NHL) and 335 controls from a previously published case-control study on malignant lymphoma are presented together with some extended analyses. No occupation was a risk factor for NHL. Exposure to phenoxyacetic acids yielded, in the univariate analysis, an odds ratio of 5.5 with a 95% confidence interval of 2.7-11. Most cases and controls were exposed to a commercial mixture of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid. Exposure to chlorophenols gave an odds ratio of 4.8 (2.7-8.8) with pentachlorophenol being the most common type. Exposure to organic solvents yielded an odds ratio of 2.4 (1.4-3.9). These results were not significantly changed in the multivariate analysis. Dichlorodiphenyltrichloroethane, asbestos, smoking, and oral snuff were not associated with an increased risk for NHL. The results regarding increased risk for NHL following exposure to phenoxyacetic acids, chlorophenols, or organic solvents were not affected by histopathological type, disease stage, or anatomical site of disease presentation. Median survival was somewhat longer in cases exposed to organic solvents than the rest. This was explained by more prevalent exposure to organic solvents in the group of cases with good prognosis NHL histopathology.

Goetz CG, Bolla KI, Rogers SM. 1994 May. Neurologic health outcomes and Agent Orange: Institute of Medicine report. Neurology 44(5):801-9.[1]Abstract: The National Academy of Sciences' Institute of Medicine conducted an independent scientific investigation to evaluate the strength of evidence for human health effects among veterans exposed to herbicides used in Vietnam and to suggest future research recommendations. Neurologic domains where multiple studies had been performed in military, occupational, or environmental situations were (1) cognitive and neuropsychiatric effects, (2) motor/coordination dysfunction and other central nervous system disorders, and (3) peripheral neuropathy. In all categories, no strong evidence established an association between herbicides used in Vietnam and clinical neurologic disorders. Methodologic weaknesses, long durations between exposure and assessments, and poor exposure measures limited many studies. The committee concluded that the available evidence was insufficient to determine an association between neurologic disorders and exposure to herbicides used in Vietnam. Neurotoxicologic studies available did not suggest strong biological plausibility for neurologic alterations related to herbicide exposure. Furthermore, given the large uncertainties in the epidemiologic studies reviewed and inadequate control for important confounders, the committee could not quantify a degree of risk for neurologic disorders from herbicide exposure likely to be experienced by Vietnam veterans. Although not part of the neurologic report, the risk of brain tumors was considered in the cancer analysis, and the committee concluded that there is limited/suggestive evidence of no association between exposure to herbicides and brain tumors.

Bullman TA, Watanabe KK, Kang HK. 1994 Jan. Risk of testicular cancer associated with surrogate measures of Agent Orange exposure among Vietnam veterans on the Agent Orange Registry. Ann Epidemiol 4(1):11-

6. Abstract: A case-control analysis was undertaken to examine the association between various surrogate measures of Agent Orange exposure and testicular cancer among Vietnam veterans. Study subjects were selected from the Department of Veterans Affairs Agent Orange Registry. The case patients consisted of 97 veterans with a diagnosis of testicular cancer, and 311 veterans without any clinical diagnosis served as a comparison group. The surrogate measures were branch of service, type of duty, corps area, and location of the individual's unit in relation to recorded Agent Orange spray tracts. Only Navy veterans had a statistically significant increased risk of testicular cancer (odds ratio (OR) = 2.60; 95% confidence interval (CI), 1.08 to 6.24). Risk of testicular cancer was not significantly increased for ground troops (OR = 0.46; 95% CI, 0.25 to 0.86), for combat duty (OR = 0.91; 95% CI, 0.52 to 1.58), for service in the III Corps area (OR = 1.10; 95% CI, 0.66 to 1.84), and for being close to spray tracts within 90 days/8 km (OR = 0.99; 95% CI, 0.54 to 1.84) or 3 days/2 km (OR = 1.39; 95% CI, 0.50 to 3.80). The study results are not consistent with the hypothesis that Agent Orange may be a risk factor for testicular cancer among Vietnam veterans.

[Anonymous]. 1994 Jan. Agent Orange and Seveso: no end in sight. Ann Oncol 5(1):4-5.

Bloemen LJ, Mandel JS, Bond GG, Pollock AF, Vitek RP, Cook RR. 1993 Dec. An update of mortality among chemical workers potentially exposed to the herbicide 2,4-dichlorophenoxyacetic acid and its derivatives. J Occup Med 35(12):1208-12. Abstract: Four years of additional mortality follow-up through 1986 are reported for a previously studied cohort of 878 chemical workers who were potentially exposed to 2,4-dichlorophenoxyacetic acid (2,4-D) and its derivatives between 1945 and 1983. Observed mortality was compared with expected levels based on death rates of the US population and of 36,804 "unexposed" workers from the same manufacturing location. Non-Hodgkin's lymphoma (NHL) was a particular focus of the study because of a suggested association with 2,4-D exposure in some case-control studies. For the total observation period, the standardized mortality ratios for all causes and for malignant neoplasms were 92 and 91, respectively. Analyses using the internal comparison group yielded virtually identical results. The initial study had found two deaths from NHL, both of which occurred under circumstances (ie, short latency and modest exposure) which made it less plausible that they were related to 2,4-D exposure. No new deaths from NHL were observed in the extended follow-up period and mortality for this cause showed a nonstatistically significant excess (standardized mortality ratio, 196; 95% confidence interval 24 to 708) for the total observation period. Analyses by production area, and by two different measures of exposure, combined with two different approaches to account for latency, did not show patterns suggestive of a causal relationship between exposure to 2,4-D or its derivatives and any particular cause of death.

Kogevinas M, Saracci R, Winkelmann R, Johnson ES, Bertazzi PA, Bueno de Mesquita BH, Kauppinen T, Littorin M, Lynge E, Neuberger M, et al. 1993 Nov. Cancer incidence and mortality in women occupationally exposed to chlorophenoxy herbicides, chlorophenols, and dioxins. Cancer Causes Control 4(6):547-53. Abstract: The association between exposure to chlorophenoxy herbicides contaminated with dioxins and occurrence of cancer has been studied mainly in male populations. In animal experiments, gender differences have been recorded in the cancer response to administered 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Mortality and cancer incidence in an international cohort of 701 women from an International Register of Workers occupationally exposed to chlorophenoxy herbicides, chlorophenols, and dioxins is examined. Cause-specific, national death rates and cancer incidence rates were used as referents. Cancer risk was not increased overall, with a standardized incidence ratio (SIR) of 96 and 95 percent confidence interval (CI) of 64-137, based on 29 cases. Among workers exposed to those chlorophenoxy herbicides contaminated with TCDD, excess cancer incidence (for all sites) was observed (SIR = 222, CI = 102-422, 9 cases); this was highest in the first 10 years after exposure. No excess was observed for breast cancer, the most common cancer in this cohort. Results on cancer mortality were consistent with those on incidence.

Ballester OF, Moscinski L, Spiers A, Balducci L. 1993 Nov. Non-Hodgkin's lymphoma in the older person: a review. J Am Geriatr Soc 41(11):1245-54. Abstract: OBJECTIVE: To study the epidemiology of non-Hodgkin's Lymphoma (NHL) in the older person and to explore treatment strategies for older persons with NHL. DESIGN: Review of the English literature. MEASUREMENTS: Incidence of NHL in patients of different ages; prevalence of NHL of different grades and stages in persons of different ages; and response to treatment, disease free survival, and survival, for patients of different ages. RESULTS: The incidence of NHL in the aged has increased approximately 80% since 1970, and approximately one-half of the 40,000

annual new cases occur in persons aged 60 and older in the USA. The 2-4 phenoxy pesticides may be partly responsible for this increment. The treatment of low grade lymphoma is mostly palliative and well tolerated by the aged. Age may have an adverse effect on the prognosis of intermediate grade lymphomas, and the prevalence of poor prognostic factors and comorbidity increases with age. Among persons aged 65-75, the complete response rate (CRR) of intermediate grade NHL to chemotherapy is approximately 50%, and approximately one-third of complete responders remain alive and free of disease 5 years from diagnosis. Among those aged 75 and older, the CRR to chemotherapy is approximately 40%, and the median duration of response is 16 months. Strategies aimed to ameliorate treatment-related toxicity include lower doses of chemotherapy, choice of drugs better tolerated by older individuals, and prevention of chemotherapy-induced toxicity. CONCLUSIONS: NHL are an increasingly common problem for older persons. Approximately 80% of older patients with low grade lymphomas and 40%-50% of those with intermediate grade lymphomas may benefit from chemotherapy. Individualized treatment, based on life expectancy and comorbidity, is the key to effective management.

Cordier S, Le TB, Verger P, Bard D, Le CD, Larouze B, Dazza MC, Hoang TQ, Abenhaim L. 1993 Sep 9. Viral infections and chemical exposures as risk factors for hepatocellular carcinoma in Vietnam. Int J Cancer 55(2):196-201.SEPAbstract: A case-control study investigating risk factors for hepatocellular carcinoma (HCC) was conducted in Hanoi, in the north of Vietnam, between 1989 and 1992. Male cases of HCC (152) diagnosed in 2 hospitals were included. Hospital controls (241) admitted mainly to abdominal surgery departments were frequency-matched to cases for sex, age, hospital and place of residence (Hanoi, province). Odds ratios adjusted for matching variables and other potential confounders were estimated using unconditional logistic regression, or exact non-parametric statistical inference when numbers were small. Positivity for hepatitis B surface antigen (HBsAg) was the main risk factor for HCC in this sample. Five subjects (3 cases, 2 controls) had been infected by hepatitis C virus (HCV), and none of them were carriers of HBsAg, giving an OR of 38 associated with HCV infection among HBsAG-negative subjects. Alcohol drinking was associated with HCC and interacted with HBsAg positivity. Agricultural use of organophosphorous pesticides (30 liters/year or more) and military service in the south of Vietnam for 10 years or more were also associated with an increased risk of HCC. This study confirms the major role played by HBV infection and its association with HCC in south-east Asia. It also suggests how other factors such as alcohol consumption or exposure to chemicals may interact with HBV infection.

Axelson O. 1993 Sep. Seveso: disentangling the dioxin enigma? Epidemiology 4(5):389-92.

Bond GG, Rossbacher R. 1993 Apr. A review of potential human carcinogenicity of the chlorophenoxy herbicides MCPA, MCPP, and 2,4-DP. Br J Ind Med 50(4):340-8.SEPAbstract: For the purpose of assessing the human carcinogenic potential of the chlorophenoxy herbicides MCPA, MCPP, and 2,4-DP, the relevant epidemiological and toxicological evidence is reviewed. These compounds have not produced tumours in animal studies conducted under current test guidelines, giving no reason to predict that they would be carcinogenic to humans. Epidemiological studies have been conducted on three continents; greater emphasis is placed on the studies reported from western Europe, however, as this has been the area of more use. Although several of these studies provide suggestive evidence of associations between exposure to chlorophenoxy compounds and increased risks for some uncommon cancers, it is inconsistent and far from conclusive. None of the evidence specifically implicates MCPA, MCPP, or 2,4-DP as human carcinogens.

Blakley BR, Gagnon JM, Rousseaux CG. 1992 Aug. The effect of a commercial 2,4-D formulation on chemical- and viral-induced tumor production in mice. J Appl Toxicol 12(4):245-9.SEPAbstract: Male CD-1 mice were exposed to a commercial formulation of 2,4-dichlorophenoxyacetic acid (2,4-D), the amine derivative, in the drinking water at concentrations ranging from 0 to 0.163% of the formulated product, equivalent to approximately 0-50 mg kg-1 day-1 2,4-D content. The effect of 2,4-D on urethan-induced pulmonary adenoma formation was evaluated following a 105-day exposure. Urethan-induced sleeping times observed following an i.p. injection of urethan (1.5 mg g-1) after 3 weeks of 2,4-D exposure were not altered by 2,4-D, indicating that 2,4-D did not influence urethan elimination. Pulmonary adenoma production, which was evaluated 84 days after urethan injection, was enhanced by 2,4-D exposure but had no effect on tumor size. The effect of 2,4-D on the incidence of spontaneous murine lymphocytic leukemia was evaluated during the 365-day treatment period. Mortality associated with the leukemia virus was not altered by 2,4-D treatment. Exposure to this commercial 2,4-D product at moderately high levels of exposure may modify

the development or expression of certain tumors in CD-1 mice. The mechanism of the co-carcinogenic or tumor-promoting activity associated with 2,4-D exposure remains to be determined.

Cantor KP, Blair A, Everett G, Gibson R, Burmeister LF, Brown LM, Schuman L, Dick FR. 1992 May 1. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. Cancer Res 52(9):2447-55. Abstract: Data from an in-person interview study of 622 white men with newly diagnosed non-Hodgkin's lymphoma and 1245 population-based controls in Iowa and Minnesota were used to measure the risk associated with farming occupation and specific agricultural exposures. Men who ever farmed were at slightly elevated risk of non-Hodgkin's lymphoma (odds ratio = 1.2, 95% confidence interval = 1.0-1.5) that was not linked to specific crops or particular animals. Elevated risks were found, with odds ratio generally 1.5-fold or greater, for personal handling, mixing, or application of several pesticide groups and for individual insecticides, including carbaryl, chlordane, dichlorodiphenyltrichloroethane, diazinon, dichlorvos, lindane, malathion, nicotine, and toxaphene. Associations were generally stronger for first use prior to 1965 than more recently, and when protective clothing or equipment was not used. Small risks were associated with the use of the phenoxyacetic acid herbicide 2,4-dichlorophenoxyacetic acid, but the risks did not increase with latency or failure to use protective equipment. Exposure to numerous pesticides poses problems of interpreting risk associated with a particular chemical, and multiple comparisons increase the chances of false-positive findings. In contrast, nondifferential exposure misclassification due to inaccurate recall can bias risk estimates toward the null and mask positive associations. In the face of these methodological and statistical issues, the consistency of several findings, both within this study and with observations of others, suggests an important role for several insecticides in the etiology of non-Hodgkin's lymphoma among farmers.

Ibrahim MA, Bond GG, Burke TA, Cole P, Dost FN, Enterline PE, Gough M, Greenberg RS, Halperin WE, McConnell E, et al. 1991 Dec. Weight of the evidence on the human carcinogenicity of 2,4-D. Environ Health Perspect 96:213-22. Abstract: The phenoxy herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) is widely used to control the growth of weeds and broadleaf plants. We convened a panel of 13 scientists to weigh the evidence on the human carcinogenicity of 2,4-D. The panel based its findings on a review of the toxicological and epidemiological literature on 2,4-D and related phenoxy herbicides. The toxicological data do not provide a strong basis for predicting that 2,4-D is a human carcinogen. Although a cause-effect relationship is far from being established, the epidemiological evidence for an association between exposure to 2,4-D and non-Hodgkin's lymphoma is suggestive and requires further investigation. There is little evidence of an association between use of 2,4-D and soft-tissue sarcoma or Hodgkin's disease, and no evidence of an association between 2,4-D use and any other form of cancer. Scientists on the panel were asked to categorize 2,4-D as a "known," "probable," "possible," or "unlikely" carcinogen or as a noncarcinogen in humans. The predominant opinion among the panel members was that the weight of the evidence indicates that it is possible that exposure to 2,4-D can cause cancer in humans, although not all of the panelists believed the possibility was equally likely: one thought the possibility was strong, leaning toward probable, and five thought the possibility was remote, leaning toward unlikely. Two panelists believed it unlikely that 2,4-D can cause cancer in humans.

Dalager NA, Kang HK, Burt VL, Weatherbee L. 1991 Jul. Non-Hodgkin's lymphoma among Vietnam veterans. J Occup Med 33(7):774-9. Abstract: In light of findings suggesting an increase in the risk for non-Hodgkin's lymphoma among men exposed to phenoxyherbicides and concerns among veterans over Agent Orange exposure, a hospital-based case-control study was undertaken to examine the association between military service in Vietnam and non-Hodgkin's lymphoma. The cases consisted of 201 Vietnam-era veteran patients who were treated in one of 172 Department of Veterans Affairs hospitals from 1969 through 1985 with a diagnosis of non-Hodgkin's lymphoma. 358 Vietnam-era veteran patients with a diagnosis other than malignant lymphoma served as a comparison group. Military service information was obtained from a review of the veteran's military personnel records. Service in Vietnam did not increase the risk of non-Hodgkin's lymphoma either in general (branch adjusted odds ratio = 1.03, 95% confidence interval = 0.70-1.50) or with increased latency period as defined as the duration in years from first service in Vietnam to hospital discharge. Surrogate measures of potential Agent Orange exposure such as service in a specific military branch, in a certain region within Vietnam, or in a combat role as determined by military occupational speciality were not associated with any increased risk of non-Hodgkin's lymphoma.

Bond GG, Bodner KM, Cook RR. 1991 Jun 15. Re: "2,4-D, 2,4,5-T, and 2,3,7,8-TCDD: an overview". Am J Epidemiol 133(12):1293-6.

O'Brien TR, Decoufle P, Boyle CA. 1991 Jun. Non-Hodgkin's lymphoma in a cohort of Vietnam veterans. Am J Public Health 81(6):758-60. Abstract: We examined the incidence of non-Hodgkin's lymphoma (NHL) in a cohort of 18,313 United States Army veterans from the Vietnam era. Diagnoses were confirmed through a review of hospital records. Among veterans who had died after discharge or who had participated in a telephone interview (8,170 Vietnam veterans and 7,564 non-Vietnam veterans), seven Vietnam veterans and one non-Vietnam veteran had developed non-Hodgkin's lymphoma (p = 0.07). As none of the NHL cases had military job titles which suggest that they were occupationally exposed to herbicides while in Vietnam, the reasons for the excess are unclear.

Adams SL, Horvat ST, Irwin AE, Junkin RW, Koreman NM, Blakley BR. 1991 Jun. The effects of Tordon 202c exposure on urethan-induced lung adenoma formation in female CD-1 mice. Vet Hum Toxicol 33(3):209-11. Abstract: Female CD-1 mice were exposed to Tordon 202c, a herbicide containing 2,4-dichlorophenoxyacetic acid and picloram, in the drinking water for 15 w at concentrations ranging from 0 to 0.3% of the product formulation. After 3 w of the 15-w treatment period, the mice received 1.5 mg/g urethan ip. Pulmonary adenoma production was evaluated 12 w later. Tordon 202c exposure produced a dose-dependent increase in tumor number, but had no effect on tumor size. Urethan-induced sleeping times which reflected the rate of urethan metabolism or excretion were altered, but a specific dose-related effect which could be correlated with tumor production was not observed. This suggests that Tordon 202c exposure influences adenoma formation by immunological mechanisms rather than by causing indirect effects on urethan metabolism or excretion.

Young AL, Reggiani GM. 1991. Re: Letter to the editor on "Agent orange and its associated dioxins: assessment of a controversy". Am J Ind Med 19(3):399-405.

Holloway M. 1990 Nov. "A great poison". Dioxin helps elucidate the function of genes. Sci Am 263(5):16, 20.

Abdellatif AG, Preat V, Vamecq J, Nilsson R, Roberfroid M. 1990 Nov. Peroxisome proliferation and modulation of rat liver carcinogenesis by 2,4-dichlorophenoxyacetic acid, 2,4,5-trichlorophenoxyacetic acid, perfluorooctanoic acid and nafenopin. Carcinogenesis 11(11):1899-902. Abstract: Using an initiation--selection--promotion protocol for induction of liver tumors in Wistar rats, the modulating action of various peroxisome proliferators on neoplasia as well as on selected biochemical parameters was studied. After treatment with diethylnitrosamine (DEN), the animals were subsequently subjected to a selection procedure involving feeding of 2-acetylaminofluorene (2-AAF), and in the middle of the 2-AAF treatment, a single necrogenic dose of carbon tetrachloride. Following a recovery period, the rats were fed a diet containing 0.1% nafenopin (NAF), 0.015% perfluorooctanoic acid (PFOA), 0.05% 2,4-dichlorophenoxyacetic acid (2,4-D), 0.05% 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) or 0.05% phenobarbital (PB) as a positive control. When the animals were killed, 7 months after initiation, the incidence of hepatocellular carcinoma was 83, 33 and 16% in the animals treated with NAF, PFOA or 2,4,5-T respectively. No cancers were observed in controls, or in the 2,4,-D groups. In comparison with controls, NAF and PFOA caused a 60-and 24-fold increase inthe peroxisomal beta-oxidation of fatty acids respectively, but only about a 2-fold increase in the catalase activity, 2,4-D and/or 2,4,5-T were much less active in this respect, giving approximately a doubling in the rate of fatty acid oxidation. The specific activity of D-amino acid and glycolate oxidases were significantly depressed, whereas the urate oxidase levels were apparently unaffected by the NAF and PFOA treatment. The results suggest that the selective induction of peroxisomal fatty acid oxidation is consistent with the hypothesis that imbalance between H2O2 overproduction and its destruction could play a role in the modulation of hepatocarcinogenesis by peroxisome proliferators.

Brown LM, Blair A, Gibson R, Everett GD, Cantor KP, Schuman LM, Burmeister LF, Van Lier SF, Dick F. 1990 Oct 15. Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. Cancer Res 50(20):6585-91. Abstract: Mortality surveys and death certificate studies have suggested an association between leukemia and farming. To investigate whether exposure to carcinogens in an agricultural setting is related to risk of leukemia, the authors conducted a population-based case-control interview study of 578 white men with leukemia and 1245 controls living in Iowa and Minnesota.

Consistent with recent mortality studies, there were slight, but significant, elevations in risk for all leukemia [odds ratio (OR) 1.2] and chronic lymphocytic leukemia (OR 1.4) for farmers compared to nonfarmers. There were no significant associations with leukemia for exposure to specific fungicides, herbicides (including 2,4-D and 2,4,5-T), or crop insecticides. However, significantly elevated risks for leukemia of greater than or equal to 2.0 were seen for exposure to specific animal insecticides including the organophosphates crotoxyphos (OR 11.1), dichlorvos (OR 2.0), and famphur (OR 2.2) and the natural product pyrethrins (OR 3.7) and the chlorinated hydrocarbon methoxychlor (OR 2.2). There were also smaller, but significant, risks associated with exposure to nicotine (OR 1.6) and DDT (OR 1.3). This finding of elevated risks for insecticides used on animals deserves further evaluation.

Wolfe WH, Michalek JE, Miner JC, Rahe A, Silva J, Thomas WF, Grubbs WD, Lustik MB, Karrison TG, Roegner RH, et al. 1990 Oct 10. Health status of Air Force veterans occupationally exposed to herbicides in Vietnam. I. Physical health. JAMA 264(14):1824-31.Abstract: The Air Force Health Study is a 20-year comprehensive assessment of the health of Air Force veterans of Operation Ranch Hand, the unit responsible for aerial spraying of herbicides in Vietnam. The study compares the health and noncombat mortality of Ranch Hand veterans with a comparison group of Air Force veterans primarily involved with cargo missions in Southeast Asia but who were not exposed to herbicides. This report summarizes the health of these veterans as determined at the third in a series of physical examinations. Nine hundred ninety-five Ranch Hands and 1299 comparison subjects attended the second follow-up examination in 1987. The two groups were similar in reported health problems, diagnosed skin conditions, and hepatic, cardiovascular, and immune profiles. Ranch Hands have experienced significantly more basal cell carcinomas than comparison subjects. The two groups were not different with respect to melanoma and systemic cancer.

Zahm SH, Weisenburger DD, Babbitt PA, Saal RC, Vaught JB, Cantor KP, Blair A. 1990 Sep. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. Epidemiology 1(5):349-56.Abstract: To evaluate the role of the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in the development of non-Hodgkin's lymphoma (NHL), we conducted a population-based, case-control study in 66 counties in eastern Nebraska. Telephone interviews were conducted with 201 white men diagnosed with NHL between July 1, 1983, and June 30, 1986, and with 725 controls. There was a 50% excess of NHL among men who mixed or applied 2,4-D (odds ratio [OR] = 1.5; 95% confidence interval = 0.9, 2.5). The risk of NHL increased with the average frequency of use to over threefold for those exposed 20 or more days per year (p for trend = 0.051). Adjusting for use of organophosphate insecticides lowered the risk estimate for frequent users (OR = 1.8), but adjustment for fungicide use increased the risk estimate (OR = 4.5). Simultaneous adjustment for organophosphates and fungicides yielded an OR of 3.1 for farmers who mixed or applied 2,4-D more than 20 days per year. Risk also increased with degree of exposure, as indicated by application method and time spent in contaminated clothing, but not with the number of years of 2,4-D use or failure to use protective equipment. Although other pesticides, especially organophosphate insecticides, may be related to NHL, the risk associated with 2,4-D does not appear to be explained completely by these other exposures.

Anderson C. 1990 Aug 9. Agent Orange: veterans sue to force study. Nature 346(6284):498.

Mahaney FX. 1990 Jun 20. Military working dogs may be a sentinel for human cancer. J Natl Cancer Inst 82(12):1002-3.

Steele EJ, Bellett AJ, McCullagh PJ, Selinger B. 1990 May. Reappraisal of the findings on Agent Orange by the Australian Royal Commission. Toxicol Lett 51(3):261-8.

Anderson GC. 1990 Apr 5. Cancer risks. War is unhealthy, US finds. Nature 344(6266):478.

Irey NS, Mullick FG, Foster WD. 1989 Jul. A morphologic study of Vietnam veterans. Mod Pathol 2(4):360-4.Abstract: The possibility that service in Vietnam has had an adverse effect on Vietnam veterans and is the cause of some of their current illnesses has been a controversial issue in the post-Vietnam period. Addressing this problem, a pathology study has been carried out at the Armed Forces Institute of Pathology (AFIP). Pathologic diagnoses found in Vietnam veterans have been compared with a control group of

contemporary veterans without Vietnam service. This has revealed no statistically significant or unexplained differences in their demographic, anatomic, or morphologic findings. The essential similarity of their disease profiles to date fails to suggest the presence of any unique environmental factor that might have acted on the Vietnam group.

[Anonymous]. 1989 Jun. NTP Toxicology and Carcinogenesis Studies of 2,4-Dichlorophenol (CAS No. 120-83-2) in F344/N Rats and B6C3F1 Mice (Feed Studies). Natl Toxicol Program Tech Rep Ser 353:1-182. Abstract: 2,4-Dichlorophenol is a chemical intermediate used principally in the manufacture of the herbicide 2,4-dichlorophenoxyacetic acid. Toxicology and carcinogenesis studies were conducted by feeding diets containing 2,4-dichlorophenol (greater than 99% pure) for 14 days, 13 weeks, or 2 years to groups of F344/N rats and B6C3F1 mice of each sex. Genetic toxicology tests were conducted in Salmonella typhimurium, mouse L5178Y lymphoma cells, and Chinese hamster ovary (CHO) cells. Fourteen-Day and Thirteen-Week Studies: In the 14-day studies, male and female rats and mice were given diets containing 2,4-dichlorophenol at concentrations up to 40,000 ppm. One high dose male mouse died before the end of the studies; no deaths occurred in any other group, and no compound-related lesions were seen at necropsy in rats or mice. In the 13-week studies, groups of 10 rats and 10 mice of each sex were fed diets containing 0, 2,500, 5,000, 10,000, 20,000, or 40,000 ppm 2,4-dichlorophenol. All rats lived to the end of the studies, whereas all mice that received 40,000 ppm died during the first 3 weeks of the studies. Final mean body weights of rats that received 20,000 or 40,000 ppm and of male mice that received 20,000 ppm were at least 10% lower than those of controls. Bone marrow atrophy in rats and necrosis and syncytial alteration (multinucleated hepatocytes) in the liver of male mice were compound-related effects. Two-year studies were conducted by feeding diets containing 0, 5,000, or 10,000 ppm 2,4-dichlorophenol to groups of 50 male rats and 50 male and 50 female mice for 103 weeks. Groups of 50 female rats received diets containing 0, 2,500, or 5,000 ppm. Body Weight and Survival in the Two-Year Studies: Mean body weights of high dose male and female rats, high dose male mice, and both dosed groups of female mice were generally lower than those of controls. No significant differences in survival were observed between any groups of rats or mice of either sex (male rats: control, 33/50; low dose, 25/50; high dose, 32/50; female rats: 34/50; 43/50; 40/50; male mice: 33/50; 32/50; 31/50; female mice: 45/50; 40/50; 43/50). The average daily feed consumption by rats in the low dose and high dose groups was 94%-97% that by the controls. The estimated daily mean consumption of 2,4-dichlorophenol was 210 or 440 mg/kg for low dose or high dose male rats and 120 or 250 mg/kg for low dose or high dose female rats. The average daily feed consumption by mice in the low dose and high dose groups was 97% and 78% of that by the controls for males and 94% and 85% for females. The estimated daily mean consumption of 2,4-dichlorophenol was 800 or 1,300 mg/kg for low dose or high dose male mice and 430 or 820 mg/kg for low dose or high dose female mice. Nonneoplastic and Neoplastic Effects in the Two-Year Studies: There were no compound-related increased incidences of neoplastic lesions in rats or mice. The incidence of mononuclear cell leukemia was decreased in dosed male rats relative to that in controls (control, 31/50; low dose, 17/50; high dose, 17/50); the incidence of malignant lymphomas was decreased in high dose female mice (4/50) relative to that in controls (12/50). Syncytial alteration of hepatocytes was observed at increased incidences in dosed male mice (11/50; 33/49; 42/48). Genetic Toxicology: The mutagenic effect of 2,4-dichlorophenol in S. typhimurium strain TA1535 was considered to be equivocal only in the presence of hamster S9; 2,4-dichlorophenol produced no increases in revertant colonies in strains TA98, TA100, or TA1537 with or without exogenous metabolic activation. 2,4-Dichlorophenol increased trifluorothymidine (Tft) resistance in the mouse L5178Y assay without metabolic activation; it was not tested with activation. In cultured CHO cells, 2,4-dichlorophenol did not induce chromosomal aberrations but did significantly increase the frequency of sister chromatid exchanges (SCEs) both in the presence and absence of S9. Audit: The data, documents, and pathology materials from the 2-year studies of 2,4-dichlorophenol have been auom the 2-year studies of 2,4-dichlorophenol have been audited. The audit findings show that the conduct of the studies is documented adequately and support the data and results given in this Technical Report. Conclusions: Under the conditions of these 2-year feed studies, there was no evidence of carcinogenic activity for male F344/N rats fed diets containing 5,000 or 10,000 ppm 2,4-dichlorophenol or for female F344/N rats fed diets containing 2,500 or 5,000 ppm 2,4-dichlorophenol. There was no evidence of carcinogenic activity for male or female B6C3F1 mice fed diets containing 5,000 or 10,000 ppm 2,4-dichlorophenol. Synonyms: 2,4-DCP; 2,4-dichlorohydroxybenzene

Bond GG, Bodner KM, Cook RR. 1989 Jan. Phenoxy herbicides and cancer: insufficient epidemiologic evidence for

a causal relationship. Fundam Appl Toxicol 12(1):172-88.Abstract: The question as to whether or not any or all of the phenoxy herbicides are carcinogenic to humans continues to be evaluated. We review the evidence available from the retrospective cohort and case-control epidemiology studies. Graphs of the individual probability densities for the odds ratios from the eight case-control studies of soft-tissue sarcoma, Hodgkin's disease, or non-Hodgkin's lymphoma demonstrate gross inconsistencies which are not likely to be attributable to chance. Early studies, conducted in Sweden, had indicated strong associations, but subsequent work from New Zealand and the United States has failed to substantiate those findings. The reasons for the discordant results may relate more to methodologic problems in the earlier studies than to qualitative or quantitative differences in the exposures of the underlying populations. The retrospective cohort studies offer the advantage of having focused on occupational groups believed to have had the highest exposures, although they have been criticized as being individually too small to assess the risks of the rarer forms of cancer. Consideration of the combined cohort studies of workers exposed to the phenoxy herbicides per se provides little or no evidence of carcinogenicity. Thus, the total weight of evidence currently available does not support a conclusion that the phenoxy herbicides present a carcinogenic hazard to humans.

Lilienfeld DE, Gallo MA. 1989. 2,4-D, 2,4,5-T, and 2,3,7,8-TCDD: an overview. Epidemiol Rev 11:28-58.

Hall W. 1989. The logic of a controversy: the case of Agent Orange in Australia. Soc Sci Med 29(4):537-44.Abstract: Since 1979 the Vietnam Veterans' Association of Australia (VVAA) has claimed that exposure to the herbicide Agent Orange in Vietnam has adversely affected the health of Vietnam veterans and their families. A campaign for government recognition of diseases and disabilities caused by herbicide exposure led in 1983 to the appointment of the Evatt Royal Commission which, after a 2-year inquiry, comprehensively rejected the VVAA's claim. The Evatt Commission's findings have not been accepted by the VVAA and the claim continues to be defended, albeit in a highly qualified form. This controversy exemplifies the way in which a claim can attract public support, and persist despite rejections by Committees of Inquiry. An understanding of the reasons for the persistence of controversy requires an understanding of the logic of rejecting causal claims, the psychology of everyday inductive reasoning, and the interaction between politics and science.

Bond GG, Wetterstroem NH, Roush GJ, McLaren EA, Lipps TE, Cook RR. 1988 Feb. Cause specific mortality among employees engaged in the manufacture, formulation, or packaging of 2,4-dichlorophenoxyacetic acid and related salts. Br J Ind Med 45(2):98-105.Abstract: Mortality is reported to the end of 1982 for 878 chemical workers potentially exposed to 2,4-dichlorophenoxyacetic acid (2,4-D) at any time between 1945 and 1983. Observed mortality was compared with expected levels based on adjusted rates for United States white men and for other male employees from this manufacturing location who were not exposed to 2,4-D. Because of a recently reported increased incidence of astrocytomas in male rats fed the highest dose level of 2,4-D, special attention was given to deaths from brain neoplasms in the cohort. None was observed. The absence of an increased risk of brain cancer in people exposed to 2,4-D is supported by studies of other exposed populations and those studies are briefly reviewed. Moreover, in the present study, analyses by production area, duration of exposure, and cumulative dose showed no patterns suggestive of a causal association between 2,4-D exposure and any other particular cause of death.

Lynge E, Storm HH, Jensen OM. 1987 Oct 15. The evaluation of trends in soft tissue sarcoma according to diagnostic criteria and consumption of phenoxy herbicides. Cancer 60(8):1896-901.Abstract: The possible association between exposure to phenoxy herbicides and development of soft tissue sarcomas has been studied in both case-control and cohort studies. In these studies soft tissue sarcoma cases have been identified from either deaths with malignant neoplasms of the connective tissue (ICD-8 171) as the underlying cause of death, from incident cancer cases with the same topography code, or from incident cases of extraskeletal sarcomas, excluding lympho and reticulosarcomas. The current study shows that the choice of source material has a considerable influence on the registered occurrence of soft tissue sarcomas in a well defined population. In 1978 to 1982 an annual number of 33 deaths from ICD-8 171 was registered in Denmark, whereas the annual number of diagnosed extraskeletal sarcomas was 231. The distribution over histologic types differed between tumours coded to the connective tissue and extraskeletal sarcomas coded to specific organs. Furthermore, during the period 1943 to 1982 the mortality from ICD-8 171 increased slightly, whereas the incidence from all extraskeletal sarcomas decreased slightly, except for

males since 1970. Time trends based on any of the three source materials should, however, be interpreted with caution.

Kang H, Enzinger FM, Breslin P, Feil M, Lee Y, Shepard B. 1987 Oct. Soft tissue sarcoma and military service in Vietnam: a case-control study. J Natl Cancer Inst 79(4):693-9.Abstract: A case-control study was conducted in men who were of draftable age during the Vietnam conflict to examine the association of soft tissue sarcomas (STSs) with military service in Vietnam as well as other host and environmental risk factors. A total of 217 STS cases selected from the Armed Forces Institute of Pathology were compared to 599 controls for Vietnam service, occupational and nonoccupational exposure to various chemicals, occupational history, medical history, and life-style (smoking, alcohol, coffee, etc.). Military service information was verified by a review of the patient's military personnel records. Other information was ascertained from a telephone interview with either subjects or their next of kin. Cases and controls were stratified on the basis of the hospital type (civilian, Veterans Administration, and military); the Mantel-Haenszel estimate of the odds ratio (OR), adjusted for the effects of the stratification variable, was calculated. Vietnam veterans in general did not have an increased risk of STS when compared to those men who had never been in Vietnam (OR, 0.85; 95% confidence interval, 0.54-1.36). Subgroups of Vietnam veterans who had higher estimated opportunities for Agent Orange exposure seemed to be at greater risk of STSs when their counterparts in Vietnam were taken as a reference group. However, this risk was not statistically significant.

Constable JD, Timperi R, Clapp R, Antman K, Boynton B. 1987 Sep. Vietnam veterans and soft tissue sarcoma. J Occup Med 29(9):726 .

Hall W. 1987 Apr 20. The Agent Orange controversy. Med J Aust 146(8):453-4.

Vineis P, Terracini B, Ciccone G, Cignetti A, Colombo E, Donna A, Maffi L, Pisa R, Ricci P, Zanini E, et al. 1987 Feb. Phenoxy herbicides and soft-tissue sarcomas in female rice weeders. A population-based case-referent study. Scand J Work Environ Health 13(1):9-17.Abstract: A population-based case-referent study was conducted in an area of northern Italy where rice growing is the predominant agricultural activity and phenoxy herbicides have been used since 1950. Manual rice weeding was formerly performed by a seasonal female working population; in the early 1950s these women were concurrently exposed to chemical herbicides. Sixty-eight persons representing incident and histologically revised cases (31 women) and 158 population referents (73 women) were interviewed. The cases were histologically confirmed independently by two blinded pathologists, and exposure to phenoxy herbicides was assessed by two blinded pesticide researchers. An age-adjusted odds ratio of 0.91 was found for the living men (with suspect exposures; no man diagnosed as a case had been exposed with certainty to phenoxy herbicides). Among the living women the relative risk was 2.7 (90% confidence interval 0.59-12.37), and it further increased when attention was restricted to women exposed in the whole 1950-1955 period and to younger age groups.

Diefenback RC. 1987 Feb. Agent Orange studies are incomplete. Occup Health Saf 56(2):67.

Lynge E. 1987. Background and design of a Danish cohort study of workers in phenoxy herbicide manufacture. Am J Ind Med 11(4):427-37.Abstract: In 1982, a Danish cohort study was initiated of workers in the manufacture of 2,4-dichlorophenol- and 4-chloro-ortho-cresol-based phenoxy herbicides, after a governmental working group had indicated the need for further data on the long-term health consequences of exposure to these phenoxy herbicides. A cohort study of workers in the manufacture of these substances was considered to be a valuable supplement to the Swedish case-control studies of patients exposed mainly in spraying. Manufacture of phenoxy herbicides was commenced in Denmark by Kemisk Vaerk Koege (KVK) in 1947, and this company has produced 2,4-D and MCPA, and later 2,4-DP and MCPP. Very limited amounts of 2,4,5-T have been processed in this plant, mainly in the formation of esters based on a purchased acid. Manufacture of MCPA was commenced by Esbjerg Kemikaliefabrik (EK) in 1951, and this production was later supplemented with 2,4-DP. Furthermore, MCPA was produced by Cheminova and Danske Gasvaerkers Tjaerekompagni for short periods in the late 1950s. All persons employed at KVK and EK from the time when these plants began operation, in 1933 and 1951 respectively, until 1982 were intended to be included in this cohort study. The registration was based on company records and, from

1964 onward, supplemented with data from a public pension scheme (ATP). Linkage of company records from KVK with ATP records for the overlapping period 1964-1980 showed 2,163 persons to be known in both datasets, whereas 614 persons were known only from the ATP records. The data collection has consequently shown that ATP provides a valuable data source for control of company records in Denmark. For the study period before 1964, the number of registered employees could be controlled by comparison with the number of employees reported by the companies on questionnaires for the national industrial statistics 1945-1969. In the analysis of this cohort study, special attention was given to soft tissue sarcomas and malignant lymphomas, which are the diagnostic groups associated with exposure to phenoxy herbicides in the Swedish case-control studies. Soft tissue sarcomas, in both organs and connective tissue, can be identified using the classifications found in the Danish Cancer Registry.

Kang HK, Weatherbee L, Breslin PP, Lee Y, Shepard BM. 1986 Dec. Soft tissue sarcomas and military service in Vietnam: a case comparison group analysis of hospital patients. J Occup Med 28(12):1215-8.Abstract: The possibility that exposure to Agent Orange or phenoxy herbicides may have increased the risk of soft tissue sarcomas has been of genuine concern to Vietnam veterans and their families. A hospital-based case comparison group study was undertaken to examine, through a comprehensive review of medical records and military personnel records, the association between previous military service in Vietnam and soft tissue sarcomas. The case group comprised 234 Vietnam-era veteran patients who served in the US military between 1964 and 1975 and were treated in one of the 172 VA hospitals between 1969 and 1983 with a diagnosis of soft tissue sarcomas. The comparison group consisted of 13,496 patients who were systematically sampled from the same Vietnam-era veteran patient population from which the cases were drawn. Military service information, in particular Vietnam service status, for each case and control patient was obtained from a review of the patient's military personnel records archived at the National Personnel Records Center in St Louis, Missouri. No significant association of soft tissue sarcomas and previous military service in Vietnam was observed: odds ratio was 0.83 with a 95% confidence interval of 0.63 to 1.09.

Hoar SK, Blair A, Holmes FF, Boysen CD, Robel RJ , Hoover R, Fraumeni JF Jr. 1986 Sep 5. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA 256(9):1141-7.Abstract: A population-based case-control study of soft-tissue sarcoma (STS), Hodgkin's disease (HD), and non-Hodgkin's lymphoma (NHL) in Kansas found farm herbicide use to be associated with NHL (odds ratio [OR], 1.6; 95% confidence interval [CI], 0.9, 2.6). Relative risk of NHL increased significantly with number of days of herbicide exposure per year and latency. Men exposed to herbicides more than 20 days per year had a sixfold increased risk of NHL (OR, 6.0; 95% CI, 1.9, 19.5) relative to nonfarmers. Frequent users who mixed or applied the herbicides themselves had an OR of 8.0 (95% CI, 2.3, 27.9) for NHL. Excesses were associated with use of phenoxyacetic acid herbicides, specifically 2,4-dichlorophenoxyacetic acid. Neither STS nor HD was associated with pesticide exposure. This study confirms the reports from Sweden and several US states that NHL is associated with farm herbicide use, especially phenoxyacetic acids. It does not confirm the case-control studies or the cohort studies of pesticide manufacturers and Vietnam veterans linking herbicides to STS or HD.

[Anonymous]. 1986 May 26. Storm in a cup of 2,4,5-T. Med J Aust 144(11):611-3.

Wiklund K, Holm LE. 1986 Feb. Soft tissue sarcoma risk in Swedish agricultural and forestry workers. J Natl Cancer Inst 76(2):229-34.Abstract: The risk of soft tissue sarcoma following possible exposure to phenoxy acid herbicides was studied in 354,620 Swedish men, who were employed in agriculture or forestry according to a national census in 1960. This cohort was further divided into six subcohorts, on assumed exposure to phenoxy acid herbicides. The most commonly used phenoxy acid in Sweden was (4-chloro-2-methylphenoxy)acetic acid (CAS: 94-74-6). The reference cohort encompassed 1,725,845 Swedish men employed in other industries. All persons were followed up in the cancer-environment register during the period 1961-79. A total of 331 cases of soft tissue sarcomas was observed in the study cohort and there were 1,508 cases in the reference group [relative risk (RR), 0.9; 95% confidence interval, 0.8-1.0]. No subcohort of agricultural or forestry workers showed any significantly increased RR, nor was there any significant difference in RR between the subcohorts. Despite the greatly increased use of phenoxy acid herbicides from 1947 to 1970, no time-related increase in the RR of soft tissue sarcoma was found in the total cohort or in any of the subcohorts.

[Anonymous]. 1986. Occupational exposures to chlorophenoxy herbicides. IARC Monogr Eval Carcinog Risk Chem Hum 41:357-406.

Tindall JP. 1985 Oct. Chloracne and chloracnegens. J Am Acad Dermatol 13(4):539-58. Abstract: Chloracne, an acneform eruption resulting from poisoning by halogenated aromatic compounds, has been a considerable problem over the last 40 years. The condition is always a symptom of systemic poisoning and should be familiar to all practitioners, particularly dermatologists. It is difficult to treat and can last for long periods without known additional exposure to chloracnegens. Some chloracnegens are capable of causing a variety of systemic signs and symptoms and may be oncogenic. Although there are probably fewer than 4,000 persons with chloracne worldwide, those found with the disorder should be evaluated medically on a regular basis and followed, if possible, throughout their lives.

Hall W, MacPhee D. 1985. The Agent Orange controversy in Australia: a contribution to the debate. Community Health Stud 9(2):109-19.

Hobson LB. 1984 Dec. Human effects of TCDD exposure. Bull Environ Contam Toxicol 33(6):696-701.

Smith AH, Pearce NE, Fisher DO, Giles HJ, Teague CA, Howard JK. 1984 Nov. Soft tissue sarcoma and exposure to phenoxyherbicides and chlorophenols in New Zealand. J Natl Cancer Inst 73(5):1111-7. Abstract: Phenoxyherbicides, including (2,4,5-trichlorophenoxy)acetic acid (CAS: 93-76-5), have been widely used in New Zealand for over 30 years. In the light of Swedish studies reporting an association between exposure to phenoxyherbicides or chlorophenols and soft tissue sarcoma, a case-control study was undertaken that involved interviewing 82 subjects (cases) with soft tissue sarcoma and 92 controls with other types of cancer. For those potentially exposed to phenoxyherbicides for more than 1 day not in the 5 years before cancer registration, the estimate of relative risk was 1.3, with 90% confidence limits of 0.6-2.5. The comparable relative risk estimate for chlorophenol exposure was 1.5, with 90% confidence limits of 0.5-4.5. The discovery of cases in trichlorophenol manufacturing plants in the United States lended support to the Swedish findings, but further studies are needed to conclude whether human exposure to these chemicals truly increases the risk of soft tissue sarcoma.

Sellar J. 1984 Aug 16-22. Agent Orange: Australian study continues. Nature 310(5978):534.

Fox JL. 1984 Mar 16. Agent Orange study is like a chameleon. Science 223(4641):1156-7.

Sarma PR, Jacobs J. 1982 May 6. Thoracic soft-tissue sarcoma in Vietnam veterans exposed to Agent Orange. N Engl J Med 306(18):1109.

[Anonymous]. 1982 Feb. Carcinogenesis Bioassay of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (CAS No. 1746-01-6) in Swiss-Webster Mice (Dermal Study). Natl Toxicol Program Tech Rep Ser 201:1-113. Abstract: 2,3,7,8-Tetrachlorodibenzo-p-dioxin occurs as a highly toxic impurity found in herbicides containing 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2,4,5-T- derivatives, as well as in other chemicals synthesized using 2,4,5-trichlorophenol. The herbicide 2,4,5-T has been marketed in the United States since 1948. Production increased sharply between 1960 and 1970 when a 1:1 mixture of 2,4,5-T and 2,4-dichlorophenoxyacetic acid (2,4-D) was used as a defoliant in Vietnam under the names of "herbicide agent orange, herbicide orange, agent orange, and orange". During this 10-year period, about 106 million pounds of 2,4,5-T were sprayed. A carcinogenesis bioassay was conducted by applying an acetone suspension of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) to the clipped backs of 30 male and female Swiss-Webster mice 3 days per week for 99 or 104 weeks. Similar groups were pretreated with 1 application of 50 &mgr;g dimethylbenzanthracene (DMBA) in 0.1 ml acetone 1 week before TCDD administration began. Female mice received 0.005 &mgr;g TCDD per application, and the male mice received 0.001 &mgr;g TCDD. As vehicle controls, 45 mice of each sex received 0.1 ml acetone three times per week. Thirty animals of each sex were used as untreated controls. Throughout the bioassay, mean body weights of the male and female mice administered TCDD, or TCDD following DMBA, were essentially the same as those of the corresponding vehicle control group. Mean body weights of dosed and vehicle control groups of males were less thanthose of the untreated control group throughout the study; for the females, mean body

weights were less than the untreated controls during the first 80 weeks. In female mice, the incidences of fibrosarcoma in the integumentary system in dosed groups with TCDD were significantly (P=0.007) higher than that in the corresponding controls (2/41, 5%; 8/27, 30%). An increase in the same tumor type, although not statistically significant (P=0.084), was also observed in the male mice (3/42, 7%; 6/28, 21%). In the DMBA-TCDD experiment, failure to have included groups skin painted with only DMBA precluded interpretation of these results. Under the conditions of this bioassay, 2,3,7,8-tetrachlorodibenzo-p-dioxin applied to the skin was not carcinogenic for male Swiss-Webster mice (the increase of fibrosarcomas in the integumentary system may have been associated with the skin application of TCDD). TCDD was carcinogenic for female Swiss-Webster mice causing fibrosarcomas in the integumentary system. Levels of Evidence of Carcinogenicity: Male Mice: Equivocal Female Mice: Positive Synonyms: 2,3,7,8-TCDD; TCDD

[Anonymous]. 1980 Aug. Bioassay of a Mixture of 1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin and 1,2,3,7,8,9-Hexachlorodibenzo-p-dioxin (Gavage) for Possible Carcinogenicity (CAS No. 57653-85-7,CAS No. 19408-74-3). Natl Toxicol Program Tech Rep Ser 198:1-187.SEPAbstract: Hexachlorodibenzo-p-dioxins (HCDD) are formed during the manufacture of certain chlorophenols. They have been found in trichlorophenol, tetrachlorophenol, and pentachlorophenol and in the chlorophenol-derived herbicides, 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). From 1967 to 1970, the concentration of HCDD in commercial pentachlorophenol ranged from 0.03 to 38 ppm. Since then, HCDD levels in pentachlorophenol have been less than 1 ppm. A bioassay of a mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-hexachlorodibenzo-p-dioxin (HCDD) for possible carcinogenicity was conducted by administering the test material by gavage to Osborne-Mendel rats and B6C3F1 mice for 104 weeks. Fifty rats and 50 mice of each sex were administered HCDD suspended in a vehicle of 9:1 corn oil-acetate 2 days per week for 104 weeks at doses of 1.25, 2.5, or 5 &mgr;g/kg/wk for rats and male mice and 2.5, 5, or 10 &mgr;g/kg/wk for female mice. Seventy-five rats and 75 mice of each sex served as vehicle controls. In addition, one untreated control group containing 25 rats and 25 mice of each sex was present in the HCDD treatment room, and one untreated control group containing 25 rats and 25 mice of each sex was present in the vehicle control room. All surviving animals were killed at 105 to 108 weeks. In rats, a dose-related depression in mean body weight gain became evident in the males after week 68 of the bioassay and in the females after week 33. In mice, the mean body weight gain in the dosed groups was comparable with that of the vehicle control groups. No other toxic clinical signs were reported in either the rats or the mice. Administration of HCDD had no adverse effect on the survival of either species. In male rats, hepatocellular carcinomas or neoplastic nodules occurred at low incidences that were dose related (P=0.003). In a direct comparison, the incidence of these tumors in the high-dose group was higher (P=0.022) than that in the corresponding vehicle-control groups, but the Bonferroni requirement of P=0.017 for the multiple comparison of three dosed groups with a control group was not met. In female rats, hepatocellular carcinomas, adenomas, or neoplastic nodules occurred at incidences that were dose related (P<0.001), and in direct comparisons the incidences of these tumors in the mid-and high-dosed groups were significantly higher (P=0.006 and P<0.001, respectively) than those in the corresponding vehicle-control group. In male mice, hepatocellular carcinomas or adenomas occurred at incidences that were dose related (P=0.001), and in a direct comparison the incidence of these tumors in the high-dose group was significantly higher (P=0.001) than that in the corresponding vehicle-control group. In female mice, hepatocellular carcinomas or adenomas occurred at incidences that were dose-related (P=0.002), and the incidence of these tumors in the high-dose group was significantly higher (P=0.004) than that in the corresponding vehicle-control group. Complex nonneoplastic toxic liver lesions were seen in all dosed groups of rats and mice. Compound-associated hyperplastic lesions of the lung were also found in both male and female rats. Under the conditions of this bioassay, HCDD administered by gavage was carcinogenic, causing increased incidences of hepatocellular carcinomas or neoplastic nodules in female Osborne-Mendel rats and inducing hepatocellular carcinomas and adenomas in male and female B6C3F1 mice. HCDD was not demonstrated to be carcinogenic for male rats. Levels of Evidence of Carcinogenicity: Male Rats: Equivocal Female Rats: Positive Male Mice: Positive Female Mice: Positive Synonym: HCDD

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Axelson O, Sundell L, Andersson K, Edling C, Hogstedt C, Kling H. 1980 Mar. Herbicide exposure and tumor

mortality. An updated epidemiologic investigation on Swedish railroad workers. Scand J Work Environ Health 6(1):73-9.Abstract: An earlier cohort study of Swedish railroad workers indicated a possible relationship between exposure to herbicides and an increased overall tumor morbidity and mortality. The cohort of 348 individuals has now been followed through October 1978. In this updated analysis of the causes of death among railroad workers, the observed number of tumor deaths was higher than expected, especially among individuals exposed in the earlier years of the study to both amitrol and phenoxy acids. However, the excess tumor mortality among persons exposed to amitrol became more moderate, and the earlier, slightly increased tumor mortality among people exposed to phenoxy acids more pronounced. No specific type of tumor predominated although there were three stomach cancers and three lung cancers. The result of the previous analysis of deaths among these railroad workers has been confirmed as to an excess of tumors, but the aspects of causal relationships to specific agents remain rather unclear, especially since workers exposed to a combination of amitrol and phenoxy acids seem to be the most seriously affected. However, the result, being in agreement with animal data and other epidemiologic studies, suggests a need for the careful handling of amitrol and phenoxy acids as increasingly suspicious carcinogens.

Hardell L, Sandstrom A. 1979 Jun. Case-control study: soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. Br J Cancer 39(6):711-7.Abstract: In 1977 a number of patients with soft-tissue sarcomas and previous exposure to phenoxyacetic acids were described. Following from these observations a matched case-control study was made. Exposure to chlorophenols was also included in this study. The results showed that exposure to phenoxyacetic acids or chlorophenols gave an approximately 6-fold increase in the risk for this type of tumour. It was not possible to determine, however, whether the carcinogenic effect was exerted by these compounds or by impurities such as chlorinated dibenzodioxins and dibenzofurans that in almost all cases were part of the commercial preparations.

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