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A Case-Control Study to Identify Agricultural Chemicals Associated with Increased Risk of Prostate Cancer and In Vitro Screening of their Endocrine Disruption Activities

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FINAL REPORT

**A case-control study to identify agricultural chemicals
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by

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Cancer Control Research

BC Cancer Agency

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Final Report

1. Research Problem

The objective of this research proposal is to identify agricultural chemicals associated with an increased risk of developing prostate cancer, and characterize the nature of their biological properties in prostatic carcinogenesis focussing on endocrine disruption properties.

The specific aims of this study are:

- 1) To identify chemical substances used in the BC agricultural industry that are associated with the risk of developing prostate cancer, and
- 2) To characterize the identified substances *in vitro* for their androgen receptor and aryl hydrocarbon receptor related activities.

In this study, the common limitation of lacking exposure details in epidemiologic studies is overcome to a certain extent through the use of the job exposure matrix (JEM) that has been recently developed for the agricultural industry in British Columbia (BC) at the BC Cancer Agency. Exposure to agricultural chemicals is individually estimated by linking the subjects' lifetime occupational histories with the JEM. The endocrine disruption properties of the identified substances are studied in collaboration with the Prostate Centre at the Vancouver General Hospital (VGH).

2. Background Context

In Canada and in the United States prostate cancer is the most common life-threatening cancer in men.^{1,2} These two countries have the highest incidence rates for prostatic cancer in the world,³ highest rates being observed among Black Americans in the United States^{3,4} and in British Columbia, Canada.⁵ The epidemiology of prostate cancer has been the object of several recent reviews;⁶⁻⁹ despite the common occurrence of this tumor, its etiology remains largely unknown; age, family history, Black American ethnicity, hormonal factors, and a high consumption of animal fat and red meat, are the most consistent risk factors reported.⁶⁻¹¹ A large number of diverse occupations have also been suggested to be associated with an increased risk for prostatic cancer including administrative, managerial, professional, health and clerical occupations, mechanics, welders, policemen and farmers, as well as workers in the metal, paint and rubber industries.^{6,7,9} Few of these associations, however, have been detected in more than one or two studies.

A fairly consistent relationship with prostate cancer has been found for farmers.^{6-8,12-17} A case-control study of 1516 prostate cancer patients in British Columbia¹⁸ identified farming occupations with elevated risks, with important confounding factors being accounted for. Exposure to pesticides, insecticides, fertilizers, herbicides and other agricultural chemicals has been suggested as a potential risk factor.¹⁹ However the cancer impact of agricultural chemicals has not been established due to the lack of information on specific exposures in epidemiologic data collected to date, except in one study.²⁰ Analyses have mainly been based on occupation or industry titles which potentially may entail a host of different chemical exposures. This type of analysis

prevents identification of specific chemical risk factors and may produce biased risk estimates.¹⁵ Thus, there is a need for better assessment of chemical exposure in epidemiologic studies.

Biologically, the development of carcinoma of the prostate is an androgen-dependent process.²¹ The prostate, which requires androgenic hormones for its growth, development, and differentiation, is responsive to androgens during fetal, pubertal, and adult life stages.²² Compounds that interfere with androgen action can cause inhibition of cellular proliferation and induction of cell death mechanisms, which results in involution of the prostate.²³ The prostate, whose hormonal sensitivity makes it vulnerable to endocrine disruptor compounds, is considered one of the most susceptible sites in the male reproductive endocrine system.²⁴ An endocrine disruptor, through the androgen receptor (AR) and the aryl hydrocarbon receptor (AhR) related activities, can alter the synthesis of steroid hormones,²⁵ or alter the transport and clearance of hormones by binding to steroid binding proteins in the serum. Environmental hormones are also known to alter steroid hormone receptor activation indirectly by down regulating the receptor or decreasing the sensitivity of the receptor to the ligand.²⁶ However, the most common known mechanism of endocrine disruption is through direct hormone receptor binding by the contaminant or its metabolites. By mimicking the natural ligand or inhibiting the natural ligand from binding to the receptor, a compound can act as a steroid hormone agonist or antagonist, respectively. This has been shown through in vitro hormone binding and transcriptional assays that demonstrated the ability of many environmental contaminants to interact at the molecular level with one or more steroid

hormone receptors.²⁷⁻²⁹ Several fungicides and pesticides have demonstrated endocrine disruption properties. Researchers at the VGH Prostate Cancer have recently completed an extensive study of the hexachlorobenzene fungicide to show the androgen receptor action *in vitro*.³⁰ The fungicide vinclozolin has been shown to alter sex differentiation in male rats.³¹ Pesticides with endocrine disrupting properties includes DDT, dieldrin and toxaphene.³²⁻³⁵ The DDT metabolite, *p, p*-DDE has been shown to bind androgen receptor and act as an antagonist in rodents and reptiles at concentrations similar to that in the environment.³⁶

This study examines *in vitro* the endocrine disruption properties of constituents in agricultural chemicals associated with increased risk of prostate cancer. Specifically we evaluate the potential interference of AR action through activation of the AhR by dioxins and other AhR ligands. To screen for AhR mediated endocrine disruption of AR, we use two highly sensitive tissue-culture-based reporter gene assay systems designed to detect compounds which may affect hormonal action of AR, and assess the activity of AhR-mediated transcription using a comparable dioxin-responsive reporter system.

This project is a part of the Occupational Oncology Research Program at the BC Cancer Agency (BCCA). It is the provincial organization responsible for coordinating cancer care and treatment as well as establishing cancer prevention programmes in the province of British Columbia. In 1983, a section of Occupational Oncology was created within the BCCA Cancer Control Research in order to address the preventive aspects of the Agency's mandate for the BC worker's population. With the collaboration of the University of British

Columbia Department of Chemical Engineering, a comprehensive research programme was initiated to identify high cancer risk occupations and potential carcinogens in the workplace, and to conduct field studies in partnership with management and labour. With respect to the first objective, identification of occupational cancer risk factors, a methodical and stepwise research programme was developed, consisting of inter-related and increasingly more specific studies ranging from broad-based hypothesis-generating investigations to cohort studies.^{18,37-55} The second objective of the programme, identification of carcinogens in the workplace, entailed the development of job-exposure matrices for the main industries of BC⁵⁶⁻⁵⁹ with the view to link these matrices to our occupational databases for analysis by chemical exposures. Use of JEMs is a significant advance over analysis by job title. As part of these projects, we have developed a comprehensive hierarchical system for coding occupational exposures which permits computerized retrieval of highly specific compounds, classes and groups of compounds.^{60,61} We have also translated the United States Industrial and Occupational classifications into the Canadian equivalent⁶² to enable linking the comprehensive job-exposure matrices developed in the United States^{63,64} to our databases. The programme also includes a service and education component to answer concerns raised by labour and management, and involves the participation of professionals with expertise in epidemiology, statistics, programming, engineering and industrial hygiene as well as highly competent grant supported personnel. The study fits under the second objective, identification of carcinogens in the workplace, of the research program. Furthermore, the endocrine disruption properties of the identified substances are characterized in collaboration with the Prostate Centre at the Vancouver General Hospital (VGH). This study combines the

resources of a strong epidemiologic group having significant experience in the conduct of population-based studies with a nationally known laboratory based prostatic carcinogenesis program.

3. Methodology

The Case-Control Study of Prostate Cancer:

As part of the Occupational Oncology Research Program, male cancer patients ascertained by the population-based British Columbia Cancer Registry (BCCR) for the years 1983 to 1990 inclusive, were sent a self-administered questionnaire requesting life-time job descriptions, occupation and industry titles, duration and period of work, as well as information on ethnic origin, education, alcohol consumption, and life-time smoking habits. During the data collection period, questionnaires were sent to all 25726 eligible male cancer cases identified by the BCCR and 15463 (60.1%) were returned of which 1519 (9.8%) were from patients having prostatic cancer. Histological confirmation of diagnosis was obtained in all cases.

Occupations and industries are coded according to the Canadian Standard Occupational Classification (SOC) and the Canadian Standard Industrial Classification (SIC) respectively.^{65,66} In the SOC, occupations are coded according to 2 digits major groups, 3 digits minor groups and 4 digits unit groups. Details on this study have been previously reported.^{18,52}

A matched case-control design is used in this project to examine the effects of exposure to chemical substances and biological agents in agricultural industry on prostate cancer development. Cases are all 1519 prostatic cancer patients. Controls are internal controls consisting of all other cancer sites, excluding lung cancer and cancers of unknown primary site, matched to the cases on age and year of diagnosis.

Exposure Assessment:

Agricultural chemical exposures for individual participants are estimated by linking each job in subjects' occupational histories with the recently-developed agricultural JEM⁵⁹, and then aggregating over all jobs to obtain their "lifetime" cumulative exposure levels. The agricultural JEM, developed for farm workers in BC, provides a retrospective exposure picture of BC agriculture, covering the period 1950-1998, and describing exposures related to 45 animal and crop commodities produced in eight growing regions of BC.

The JEM has two axes: one for the job titles and the other for the exposures. For compatibility with epidemiological data collected by the BCCA, job titles in the JEM are based on the SIC and SOC -1980 classifications.^{65,66} Six job titles from the SOC were used. Modifications to the SIC were made to allow differentiation between specific crops. For instance the 4 digit unit/class code for fruit farms in the SIC is 0151 which includes all tree fruits, berries and grapes; an extra digit to 0151-1 is added, for example, to specify blueberries. Forty five crop and animal commodities are assessed; 30 of these are modified codes.

The axis for exposures includes chemical, biological and selected physical exposures. Pesticides, the majority of chemical exposures, are coded by active ingredient to identify the primary function (i.e. insecticide, fungicide etc) as well as by category (i.e. organophosphate, organochlorine etc.) Because many different products use the same active ingredient, to avoid duplicate codes, active ingredient rather than trade name is used. Although most products also contain various additives (solvents, spreaders, inert components etc.), these are not identified because proprietary rights allow companies to withhold this information.

Each cell of the JEM contains an exposure assessment for every combination of “type of work”, exposure and time. Pesticides were assessed either quantitatively if data are available, or by a dichotomous variable (exposed/unexposed). The calculation used for quantitative assessment depends on whether the exposure occurred during re-entry tasks (harvesting or thinning) or application tasks (mixing/loading/ spraying). A standard exposure model with some modifications is used for re-entry tasks.^{68,69} Application exposures are quantified using exposure estimates derived from the North American Pesticide Handlers Exposure Database (PHED).⁷⁰

Assessments are made to 290 different agents; of these, approximately 180 are pesticides, including 68 insecticides, 39 fungicides and 53 herbicides with the remainder coded as fumigants, rodenticides and plant growth regulators. The other assessments include

biologicals and maintenance chemicals. Details on the development of this JEM have been previously published⁵⁹.

In-Vitro Experiment - Screening for interference of AR action by putative AhR

ligands:

The *in-vitro* bio-chemical experiments are conducted at the Prostate Centre at the Vancouver General Hospital. This centre is a nationally known multidisciplinary research facility which seeks to improve the scientific understanding of the regulation and function of the prostate. Its ultimate goal is to develop novel therapies and innovative preventative approaches for prostate cancer and disease. Several research developments are relevant for this project.⁷¹⁻⁷⁴

Specifically, a highly sensitive tissue culture assay system has been developed to detect ligands which interact with AR in two human prostate cell lines, PC3 and LNCAP. This system utilizes a luciferase reporter gene construct linked to DNA sequences that can be transcriptionally activated by AR.^{72,73} Human prostate cancer cells are grown in monolayer culture and transiently transfected with three DNA plasmid constructs. The first plasmid, CMV-AR, encodes the AR under the control of a cytomegalovirus (CMV) promoter. The second plasmid, ARR3-Luc, carries the firefly luciferase reporter gene under the control of a modified androgen responsive enhancer element originating from the rat probasin gene promoter. The third plasmid, pRL-TK (Promega) comprises the renilla luciferase gene under the control of a thymidine kinase promoter, and acts as an internal control. If a recombinantly expressed AR is exposed to an agonist ligand such as

dihydrotestosterone (DHT), then the receptor-ligand complex binds to the regulatory region of the ARR3-Luc reporter gene and induces transcription. The amount of firefly luciferase protein produced in response to hormonal stimulation is assayed by mixing the crude cellular extract with commercial dual luciferase reagents (Promega) and subsequent light emission is quantified using a Microtitre Plate Luminometer (EG&G Berthold)⁷¹⁻⁷³ and normalized for renilla luciferase levels. This results in a ligand-concentration related induction. With a physiological dose of DHT (1.5nM) in PC-3 cells a 250-fold increase of luciferase expression is observed.

To assess agonistic activity of a compound, the transfected cells are exposed to a test compound, or to DHT as a control. After 24 hours, cells are harvested, lysed, and the cytosol is assayed for luciferase activity. To measure the presence and potency of a weak agonist or antagonist of AR, PC3 cells expressing an AR gene and the luciferase reporter construct are exposed to a concentration of DHT (1nM) that results in a half maximal induction of luciferase expression. The addition of increasing concentrations of an anti-androgen such as cyproterone acetate results in a corresponding decrease in the measured luciferase response. By comparing the AR response with DHT alone to AR response with DHT plus increasing concentrations of experimental compounds, very dilute concentrations of ligands that bind to AR and act as weak agonists or antagonists can be detected. Using these approaches, several compounds have thus far been identified to act either as agonists or antagonists of the AR and AhR reporter system. If a compound has significant levels of interference at biologically relevant levels of exposure then the compound will be considered for future *in vivo* and animal studies.

In this study, the general framework described above is used to study the substances identified in the case-control study. The substances are first dissolved in soluble solution to facilitate delivery of compounds into aqueous cell culture conditions. Methanol, the most desirable solvent due to its non-toxic property *in vitro*, is used. In some cases, the substances are first dissolved in ether, then further dilutions are prepared in methanol. The final concentration of solvents *in vitro* is less than 1%. Dose response curves are obtained with the substances under investigation in the presence or absence of DHT in order to characterize agonist and antagonist activity of the environmental samples. The compounds are tested *in vitro* to assess the endocrine-like effects of putative AhR ligands for agonist or antagonist activity of AR and AhR using the respective tissue culture-based reporter systems described below. To determine if a compound affects AR-mediated transcription we transfect LNCaP cells with AR, an androgen-responsive promoter linked to Luciferase (ARR3-Luc) and an internal control plasmid (pRLTS) to monitor transfection efficiency and general toxicity. Following 24 hour incubation with a range of test compound concentrations in the presence or absence of DHT, Luciferase activity is quantified and normalized to the internal reporter. To monitor AhR activity, we transfect LNCaP cells expressing endogenous AhR and ARNT proteins with a xenobiotic-responsive promoter linked to a renilla reporter gene (Gudluc 1.1) and monitor the reporter activity as before. The approach is based on the Promega Dual-Luciferase™ reporter assay system (Figure 1). This approach allows us to assess the AR and AhR activities. To confirm AR binding we perform competitive ligand binding assays using a purified recombinant AR-Ligand Binding Domain (Panvera Corp.), ³H-R1881 and

increasing concentrations of chemical substances. Relative binding affinity is determined by quantification of displacement of the ^3H -R1881 from the receptor. These systems constitute a rapid and systematic approach for the detection of endocrine disrupting substances.

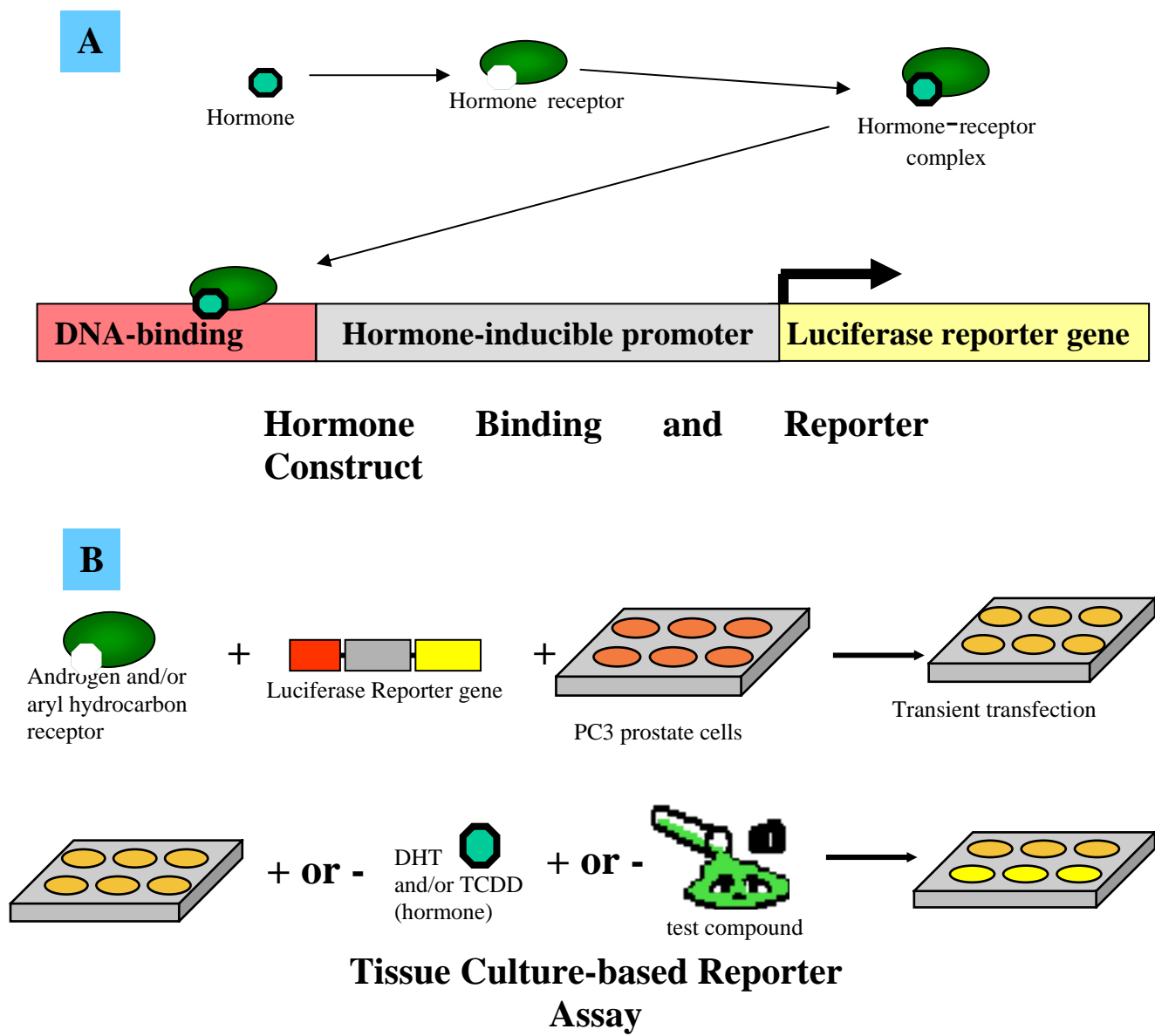


Figure 1. Tissue culture-based reporter assay used to measure potency of endocrine disruptors. Panel A) The effect of a steroid hormone is mediated by its cognate receptor to activate transcription upon binding to the hormone-responsive gene. Our experimental approach utilizes DNA constructs containing these hormone-responsive binding sites connected to a Luciferase reporter gene. **Panel B)** PC3 cells are transfected with a hormone-responsive Luciferase gene and the AR or AhR or both receptors. The cells are then incubated in the presence or absence of the natural ligand and a range of test compound concentrations. The production of Luciferase is proportional to the degree of transcriptional activity induced by the ligand-bound receptor.

Statistical Analysis:

For the case-control component, conditional logistic regression for matched sets data and the likelihood ratio test are used⁷⁵ in a 2 step procedure. In step 1, the effects of the following non-occupational confounding variables are individually assessed: marital status; education (less than 8 years; 8 to 11 years; high school; post-secondary); smoking (age started smoking, average number of cigarettes, pipe or cigars smoked per day, total years smoked; alcohol consumption (starting age at consuming alcohol; average number of bottles of beer, glasses of wine, ounces of spirits per day; total years of consuming alcohol); person who filled out the questionnaire (self or proxy). Variables are selected in a forward fashion each being examined separately; potentially important ones ($p_value < .2$) are included in the model and the remaining ones examined; the process is repeated until no potentially important confounding factor is identified. The cutpoint of 20% for the p_value is used to ensure that there is sufficient power to detect important confounding factors.

In step 2, each agricultural chemical/biological exposure is assessed separately using conditional logistic regression where all significant confounding variables identified in step 1 are taken into account. Due to the uncertainty associated with the agricultural chemical exposure of the subjects who only had agricultural jobs outside BC (89 cases and 219 controls), these subjects are removed from the analyses to avoid potential biases. Matched case-control analyses will be carried out using the SAS software;⁷⁶ test of

significance of the adjusted odds ratios (ORs) and 95% confidence intervals are calculated. Analyses are performed for exposure classified as ever and never. Dose-response relationships are also examined for the substances showing significantly increased OR's in the ever/never analysis. For each substance, an exposure index with unexposed, low and high levels is developed based on the participants' cumulative exposure. The cutpoint for low and high level is selected to have approximately 50 percent of the exposed controls in each group.

For the in-vitro experiments, individual substances are tested in triplicate for each experiment and at least two replicates. The analysis of variance approach is used to examine the endocrine disruption activities.

4. Results

The Case-Control Study:

The data from the BC case-control study discussed above (1516 cases and 4994 controls) are used in this project. Among the 515 cancer patients who ever worked in agricultural occupations, 426 patients (83%) had agricultural jobs in BC and 89 (17%) never had agricultural jobs in BC. A total of 1181 controls (84%) out of 1400 controls ever worked in agricultural occupations, had BC agricultural jobs and 219 (16%) did not.

Odds ratios (OR) and the corresponding 95% confidence intervals (CI) for ever exposed in comparison with never exposed are presented in Table 1 for substances with at least 3 exposed cases. The estimates are adjusted for potentially important confounders including alcohol consumption, cigarette years, education level, pipe years and who

responds to the questionnaire. Several significantly elevated OR's are observed, including 2,4D (OR=2.58; 95% CI: 1.08-6.20); 2,4-DB (OR=1.77; 95% CI: 1.04-3.01); Azinphos-methyl (OR=1.62; 95% CI: 1.07-2.48); Captan+Lindane (OR=4.72; 95% CI: 1.56-14.26); Captan (OR=1.53; 95% CI: 1.10-2.12); Carbaryl (OR=1.53; 95% CI: 1.08-2.16); DDT (OR=1.45; 95% CI: 1.01-2.09); Dichlone (OR=1.70; 95% CI: 1.08-2.70); Difenzoquat (OR=3.40; 95% CI: 1.03-11.26); Dinoseb amine (OR=1.71; 95% CI: 1.07-2.73); Dodine (OR=1.72; 95% CI: 1.08-2.75); Ferbam (OR=1.55; 95% CI: 1.01-2.38); Tribasic copper sulfate (OR=10.44; 95% CI: 1.20-91.13); Maneb (OR=1.57; 95% CI: 1.02-2.41); MCPA (OR=1.68; 95% CI: 1.03-2.75); Simazine (OR=1.64; 95% CI: 1.06-2.52); Organic dust (OR=1.37; 95% CI: 1.00-1.86); Natural gas (OR=1.93; 95% CI: 1.28-2.92).

Odds ratios and the corresponding 95% confidence intervals for the dose-response relationships are provided in Table 2 for those identified above. Evidence of a dose-response relationship is observed for most substances, except for Captan+Lindane where OR=.98 (95% CI: 0.09-10.86) is seen for the high-exposure level; Difenzoquate where no case is seen for the high-exposure level; and Organic dust where OR=1.14 (95% CI: 0.72-1.79) is seen for the high-exposure level. The lack of evidence for a dose-response relationship suggests that exposure to these substances is unlikely to be associated with the development of prostate cancer. For the remaining substances, further examination is warranted as discussed below.

In-Vitro Experiments:

The results for cell culture experiments using LNCap AR/DHT system are displayed in Figure 2. Several substances identified in the case-control study indicate their ability to act as androgen agonists (> 100% control luciferase activity) including Captan (p_value <.1), Dichlone (p_value < .01), Carbaryl (p_value <.01), dodine (p_value <.1), and DDT (p_value <.1).

The results for in-vitro AhR/TCDD (dioxin) activation experiments are displayed in Figure 3. The statistically significant agonists include Dichlone (p_value <.05), Carbaryl (p_value <.01), DDT (p_value <.01). The statistically significant antagonist is Dodine (p_value <.01).

The results of AR-Ligand binding assays experiments are displayed in Figure 4. The substances indicating their ability to bind to AR/AhR include Dichlone, DDT, and Dodine.

5. Implications for Future Research

The results from the case-control study indicate that a small subset of substances used in agricultural industry showing statistically significant associations with the risk of developing prostate cancer. It is important to investigate whether the substances act individually or synergistically in the development of prostate cancer in men.

Unfortunately this line of epidemiologic investigation is generally not possible from this data set. Further examination of the exposed participants to these identified substances shows that the participants once exposed to one substance during their work history, tend

to be exposed to several others as well as displayed in Table 3. For examples, out of 109 participants ever exposed to Azinphos-methyl, 108 were also exposed to Captan and 103 to Carbaryl. All of 87 participants ever exposed to Dodine were also exposed to Captan, Carbaryl, and Azinphos-methyl. Similar patterns are seen for Ferbam, Maneb, Simazine, 2,4D, 2,4-DB, Dichlone, etc. Thus although the results implicate a small subset of substances used in agricultural industry in the development of prostate cancer in men, it is generally not possible to use this data set to examine whether a specific substance acting alone or a combination synergistically affecting the development.

The results from *in-vitro* experiments also indicate that some substances demonstrate their ability to individually generate endocrine-disruption activities which may have effects on the prostate cancer development. These include Carbaryl, DDT, Dichlone and Dodine. It is possible through this line of investigation to examine the effects of combinations of substances. The findings of this study could be used for in planning future *in vivo* studies examining prostate-specific chloramphenicol acetyltransferase reporter in a probasin-transgenic mouse and to assess the effects of these substances on androgen-regulated processes and prostate cancer progression.

Ultimately, the epidemiologic knowledge gained from understanding the impact of specific agricultural chemicals on prostate cancer and the better understanding of how these substances contribute to cancer development may lead to effective strategies for the prevention of occupationally related exposure.

6. Dissemination/Knowledge Transfer

- Several research articles will result from this study. Two manuscripts are being prepared for peer-reviewed publications
- The findings will be presented at the seminar series at the WCB organized by the Research Secretariat, as well as future scientific conferences.

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TABLE 1: Adjusted OR for Ever-Never Exposure

Active Ingredient	Control	Case	O.R. ¹		95% C. I.		
1,3-DICHLOROPROPENE	19	6	0.91		0.35	-	2.39
2,4-D	12	11	2.58	*	1.07	-	6.19
2,4-DB	42	24	1.77	*	1.04	-	3.01
3,5-DINITRO-O-CRESOL	80	36	1.45	?	0.95	-	2.21
ALACHLOR	21	8	1.26		0.53	-	3.02
ALDICARB	12	4	1.15		0.35	-	3.82
ALDRIN	30	8	1.02		0.45	-	2.32
AMMONIA	26	10	1.37		0.63	-	2.98
ATRAZINE	24	9	1.44		0.63	-	3.25
AZINPHOS-METHYL	71	38	1.62	*	1.07	-	2.48
BACILLUS THURINGIENSIS	52	26	1.51		0.92	-	2.49
BARBAN	4	6	3.95	?	0.99	-	15.71
BENOMYL + CAPTAN + LINDANE	3	5	3.64	?	0.83	-	15.95
BENOMYL + THIRAM + LINDANE	3	5	3.64	?	0.83	-	15.95
BENOMYL	66	29	1.24		0.78	-	1.97
BENTAZON + ATRAZINE	19	8	1.44		0.59	-	3.50
BHC OR GAMMA HCH OR LINDANE	70	33	1.43		0.92	-	2.23
BROMOXYNIL + MCPA	29	15	1.76	?	0.90	-	3.43
BUTYLATE + CROP PROTECTANT	13	6	1.70		0.61	-	4.72
CAPTAN + DIAZINON + LINDANE	4	3	2.93		0.60	-	14.33
CAPTAN + LINDANE	5	10	4.72	**	1.56	-	14.26
CAPTAN	131	62	1.53	*	1.10	-	2.12
CARBARYL + NAA	30	15	1.39		0.72	-	2.68
CARBARYL	119	54	1.53	*	1.08	-	2.16
CARBATHIIN + THIRAM + LINDANE	5	6	3.29	?	0.91	-	11.91
CARBATHIIN + THIRAM	17	10	1.97		0.85	-	4.58
CARBOFURAN	22	6	0.86		0.33	-	2.23
CHLORANIL	32	6	0.69		0.28	-	1.71
CHLORDANE	23	6	0.94		0.37	-	2.41
CHLOROTHALONIL	31	6	0.66		0.27	-	1.63
CHLOROXYURON	14	6	1.22		0.44	-	3.34
CHLORPROPHAM	26	5	0.70		0.26	-	1.89
CHLORPYRIFOS	30	11	1.31		0.63	-	2.72
COPPER OXYCHLORIDE	81	37	1.43	?	0.94	-	2.17
COPPER SULFATE	91	39	1.31		0.63	-	2.72
CYANAZINE	19	8	1.44		0.59	-	3.50
CYHEXATIN	51	23	1.29		0.77	-	2.18
1,2- DICHLOROPROPANE + 1,3-DICHLOROPROPENE	16	10	2.08	?	0.90	-	4.82
DBCP	11	6	1.60		0.56	-	4.58
DDT	113	49	1.45	*	1.01	-	2.09
DELTAMETHRIN	19	6	0.96		0.37	-	2.50
DEMETON	16	4	0.88		0.27	-	2.82
DIAZINON	108	47	1.39	?	0.96	-	2.01
DICAMBA + MCPA	3	3	2.49		0.48	-	12.87
DICAMBA	23	14	2.02	?	0.99	-	4.13
DICHOLOBENIL	21	13	1.87	?	0.89	-	3.91
DICLOFOP-METHYL	19	6	1.20		0.45	-	3.20
DICHLONE	58	32	1.70	*	1.08	-	2.70
DICHLORVOS	86	25	0.91		0.57	-	1.46
DICOFOL	15	5	0.92		0.32	-	2.64
DIELDRIN	23	6	0.95		0.37	-	2.45
DIFENZOQUAT	6	7	3.40	*	1.03	-	11.26
DIMETHOATE	118	50	1.32		0.92	-	1.88
DINOCAP	16	6	1.24		0.46	-	3.33
DINOSEB AMINE	57	31	1.71	*	1.07	-	2.73
DINOSEB	1	5	10.44	*	1.20	-	91.13
DIQUAT	24	8	1.18		0.51	-	2.74
DISULFOTON	23	6	1.00		0.39	-	2.57

TABLE 1: Adjusted OR for Ever-Never Exposure

Active Ingredient	Control	Case	O.R. ¹		95% C. I.		
DODINE	56	31	1.72	*	1.08	-	2.75
ENDOSULFAN	85	39	1.46	?	0.97	-	2.20
EPTC + CROP PROTECTANT	29	13	1.56		0.77	-	3.15
EPTC	31	12	1.29		0.63	-	2.63
ETHEPHON	29	14	1.35		0.69	-	2.67
ETHION	59	23	1.22		0.73	-	2.03
FENSULFOTHION	15	3	0.73		0.20	-	2.69
FERBAM	73	35	1.55	*	1.01	-	2.38
FONOPHOS	17	5	1.14		0.39	-	3.28
FORMALDEHYDE	126	49	1.24		0.87	-	1.77
GIBBERELIC ACID	29	13	1.22		0.61	-	2.44
GLYPHOSATE	60	25	1.30		0.79	-	2.15
HEPTACHLOR	22	5	0.79		0.29	-	2.19
IPRODIONE	45	16	1.01		0.56	-	1.84
METHYL ISOTHIOCYANATE	22	8	1.18		0.50	-	2.78
TRIBASIC COPPER SULFATE	1	5	10.44	*	1.20	-	91.13
LINURON	27	8	0.96		0.42	-	2.22
MALATHION	207	82	1.31	?	0.99	-	1.73
MANCOZEB	81	33	1.31		0.85	-	2.02
MANEB	73	35	1.57	*	1.02	-	2.41
MCPA	54	28	1.68	*	1.03	-	2.75
MCPA + MCPB	13	3	0.97		0.26	-	3.66
MERCURY	13	11	2.28	?	0.97	-	5.38
METALAXYL + MANCOZEB	12	3	1.00		0.26	-	3.84
METALDEHYDE	27	9	1.18		0.53	-	2.62
METAM SODIUM	21	6	0.92		0.35	-	2.41
METHAMIDOPHOS	18	5	0.99		0.35	-	2.84
METHOMYL	21	4	0.64		0.21	-	1.97
METIRAM	53	24	1.38		0.83	-	2.30
METOBROMURON	10	3	1.16		0.29	-	4.58
METOLACHLOR + ATRAZINE	17	7	1.35		0.52	-	3.50
METOLACHLOR	17	7	1.35		0.52	-	3.50
METRIBUZIN	14	4	0.99		0.31	-	3.20
MEVINPHOS	24	5	0.75		0.27	-	2.06
MONOLINURON	10	3	1.16		0.29	-	4.58
NAA	43	20	1.39		0.79	-	2.43
NALED	25	6	0.87		0.34	-	2.21
PARAQUAT	73	33	1.39		0.90	-	2.15
PARATHION	63	30	1.44		0.91	-	2.29
PERMETHRIN	35	16	1.70	?	0.91	-	3.20
PHOSALONE	26	9	0.97		0.44	-	2.14
PIRIMICARB	28	6	0.75		0.30	-	1.86
PROMETRYNE	17	4	0.87		0.28	-	2.73
PROPARGITE	43	19	1.24		0.70	-	2.19
PROPYZAMIDE	7	3	1.00		0.24	-	4.19
ROTENONE	27	4	1.24		0.70	-	2.19
SIMAZINE	70	36	1.64	*	1.06	-	2.52
SODIUM FLUOSILICATE	12	5	1.23		0.41	-	3.70
SODIUM HYPOCHLORITE	113	43	1.22		0.84	-	1.77
STODDARD SOLVENT	24	4	0.65		0.22	-	1.95
TOXOPLASMOZA GONDII	11	6	1.63		0.58	-	4.57
SULPHUR	98	45	1.46	?	1.00	-	2.12
TETRADIFON	16	5	0.99		0.34	-	2.85
THIABENDAZOLE	16	4	0.86		0.27	-	2.72
THIONAZIN	16	4	0.98		0.31	-	3.13
THIOPHANATE-METHYL	42	19	1.31		0.73	-	2.33
THIRAM	30	8	0.94		0.42	-	2.13
TRIFLURALIN	37	19	1.69	?	0.93	-	3.04

TABLE 1: Adjusted OR for Ever-Never Exposure

Active Ingredient	Control	Case	O.R. ¹		95% C. I.		
ZINEB	46	7	0.52		0.23	-	1.18
ZIRAM	81	36	1.44	?	0.94	-	2.19
POTASSIUM MONOPERSULFATE	33	19	1.78	?	0.98	-	3.24
MINERAL OIL	62	31	1.56	?	0.98	-	2.47
MALEIC HYDRAZIDE	19	5	0.94		0.33	-	2.65
DAZOMET	20	3	0.50		0.14	-	1.75
DAMINOZIDE	31	13	1.15		0.58	-	2.28
AFLATOXIN B1	87	28	1.04		0.66	-	1.63
ANTIBIOTICS	157	59	1.22		0.89	-	1.69
BASIC G	11	6	1.63		0.58	-	4.57
CHLORHEXIDENE	91	30	1.07		0.69	-	1.66
CHLORINE BLEACH	87	28	1.04		0.66	-	1.63
COPPER NAPHTHENATE	11	6	1.63		0.58	-	4.57
COPPER TOX	25	11	1.48		0.70	-	3.14
COXIDIOSTATS	155	57	1.20		0.86	-	1.66
ENDOTOXIN	157	59	1.22		0.89	-	1.69
COXIELLA BURNETII	26	11	1.46		0.69	-	3.07
FENTHION	38	16	1.42		0.77	-	2.63
CALCIUM HYDROXIDE	31	11	1.20		0.58	-	2.47
HYDROGEN SULFIDE	111	44	1.28		0.88	-	1.86
INORGANIC DUST	153	59	1.24		0.90	-	1.71
IODINE	95	34	1.17		0.77	-	1.78
METHANE	111	44	1.28		0.88	-	1.86
MOULDS	157	59	1.22		0.89	-	1.69
NA CHLORITE + LACTIC ACID + CHLOROUS ACID	87	28	1.04		0.66	-	1.63
ORGANIC DUST	158	67	1.37	*	1.00	-	1.86
CHLAMYDIA PSITTACI	41	21	1.63	?	0.93	-	2.86
PHOSPHORIC ACID + SULFURIC ACID	87	28	1.04		0.66	-	1.63
POTASSIUM HYDROXIDE + NA HYPOCHLORITE	87	28	1.04		0.66	-	1.63
QUARTENARY AMMONIUM COMPOUNDS	32	11	1.24		0.60	-	2.55
ROTENONE + SULFUR	118	34	0.93		0.62	-	1.39
TETRACHLORVINPHOS	34	11	1.14		0.56	-	2.33
ZINC SULFATE + FORMALIN	25	11	1.48		0.70	-	3.14
ZINC SULFATE	25	11	1.48		0.70	-	3.14
PHENOLIC	33	19	1.78	?	0.98	-	3.24
BACILLUS ANTHRACIS (ANTHRAX)	135	52	1.25		0.89	-	1.77
BOROFORM	11	6	1.63		0.58	-	4.57
ECTHYMA (ORF)	25	11	1.48		0.70	-	3.14
FUNGAL SPORES	157	54	1.22		0.89	-	1.69
AVIAN PARAMYXOVIRUS	41	21	1.63	?	0.93	-	2.86
HC 10	11	6	1.63		0.58	-	4.57
ANTHELMINTICS	26	11	1.46		0.69	-	3.07
PSEUDOCOWPOX (MILKER'S NODE)	87	28	1.04		0.66	-	1.63
DIMETHYL BENZYL AMMONIUM CHLORIDE	11	7	2.19		0.80	-	6.05
LISTERIA MONOCYTOGENES	134	51	1.23		0.87	-	1.74
HISTOPLASMA CAPSULATUM	41	21	1.63	?	0.93	-	2.86
CARBON MONOXIDE	111	52	1.38	?	0.97	-	1.97
COMBUSTION PRODUCTS (GENERAL)	143	62	1.32	?	0.96	-	1.83
DIESEL FUEL	143	62	1.32	?	0.96	-	1.83
GASOLINE	85	37	1.28		0.85	-	1.93
GREASES (GENERAL)	143	62	1.32	?	0.96	-	1.83
KEROSENE	124	55	1.36	?	0.97	-	1.91
LUBRICATING OILS (GENERAL)	143	62	1.32	?	0.96	-	1.83
NATURAL GAS	65	43	1.93	**	1.28	-	2.92
PAINTS	81	34	1.22		0.80	-	1.86
RADIATION (SOLAR)	125	56	1.38	?	0.98	-	1.94
RADIATION (WELDING ARC)	126	56	1.37	?	0.98	-	1.92
TREATED WOOD (OTHER)	77	33	1.43		0.93	-	2.21

TABLE 1: Adjusted OR for Ever-Never Exposure

Active Ingredient	Control	Case	O.R. ¹		95% C. I.		
WELDING (GENERAL)	126	56	1.37	?	0.98	-	1.92
CAMPYLOBACTER FETUS	134	51	1.23		0.87	-	1.74
SALMONELLA SAINT-PAUL	41	21	1.63	?	0.93	-	2.86
VACCINE	145	63	1.34	?	0.98	-	1.85
HANTAVIRUS	32	19	1.83	?	1.00	-	3.34

¹ Adjusted for alcohol consumption, cigarette years, education level, pipe years, and respondent
? = p<0.10; * = p<0.05; ** = p<0.01

TABLE 2: Adjusted OR for unexposed, low, and high exposure levels

Active Ingredient	Control	Cases	O.R. 1		95 % C.I.		
2,4-D							
No	4982	1505	1.00				
Low	6	1	0.47		0.05 -		4.16
High	6	10	4.73**		1.58 -		14.16
2,4-DB							
No	4952	1492	1.00				
Low	21	8	1.17		0.50 -		2.75
High	21	16	2.36*		1.19 -		4.71
Azinphos-methyl							
No	4923	1478	1.00				
Low	35	17	1.63		0.87 -		3.06
High	36	21	1.62?		0.92 -		2.85
Captan + Lindane							
No	4989	1506	1.00				
Low	3	9	7.61**		1.98 -		29.33
High	2	1	0.98		0.09 -		10.86
Captan							
No	4863	1454	1.00				
Low	66	26	1.41		0.87 -		2.30
High	65	36	1.63*		1.06 -		2.51
Carbaryl							
No	4875	1462	1.00				
Low	59	24	1.55?		0.93 -		2.58
High	60	30	1.50?		0.94 -		2.40
DDT							
No	4881	1467	1.00				
Low	57	18	1.22		0.69 -		2.15
High	56	31	1.65*		1.03 -		2.63
Dichlone							
No	4975	1510	1.00				
Low	29	15	1.89?		0.96 -		3.71
High	29	17	1.56		0.84 -		2.92
Difenzoquat							
No	4988	1509	1.00				
Low	4	7	3.84*		1.080 -		13.740
High	2	0	0.00				
Dinoseb Amine							
No	4937	1485	1.00				
Low	29	14	1.48		0.75 -		2.92
High	28	17	1.95*		1.03 -		3.70
Dodine							
No	4938	1485	1.00				

TABLE 2: Adjusted OR for unexposed, low, and high exposure levels

Active Ingredient	Control	Cases	O.R. 1		95 % C.I.		
Low	28	14	1.90	?	0.96	-	3.79
High	28	17	1.58		0.84	-	2.99
Ferbam							
No	4921	1481	1.00				
Low	36	12	1.27		0.63	-	2.54
High	37	23	1.76	*	1.02		3.05
Maneb							
No	4921	1481	1.00				
Low	36	12	1.31		0.65	-	2.65
High	37	23	1.75	*	1.01	-	3.03
MCPA							
No	4955	1494	1.00				
Low	20	10	1.62		0.72	-	3.63
High	19	12	1.95	?	0.90	-	4.25
Simazine							
No	4924	1480	1.00				
Low	35	14	1.43		0.73	-	2.78
High	35	22	1.81	*	1.03	-	3.17
Organic Dust							
No	4837	1457	1.00				
Low	79	31	1.31		0.84	-	2.04
High	78	28	1.14		0.72	-	1.79
Natural Gas							
No	4929	1473	1.00				
Low	33	25	1.96	*	1.14	-	3.39
High	32	18	1.89	*	1.02	-	3.51

1 Adjusted for alcohol consumption, cigarette years, education level, pipe years, and respondent.

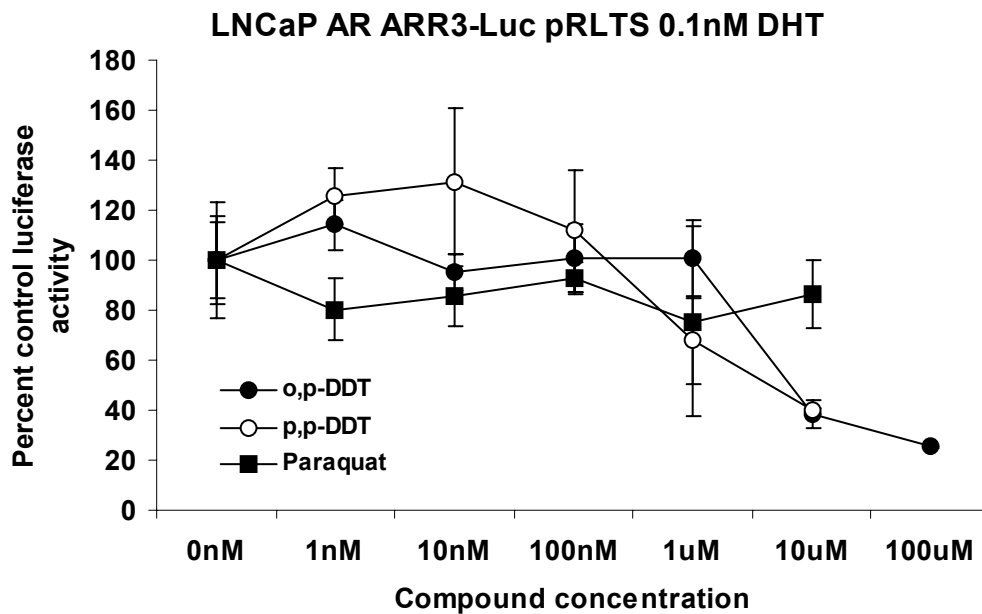
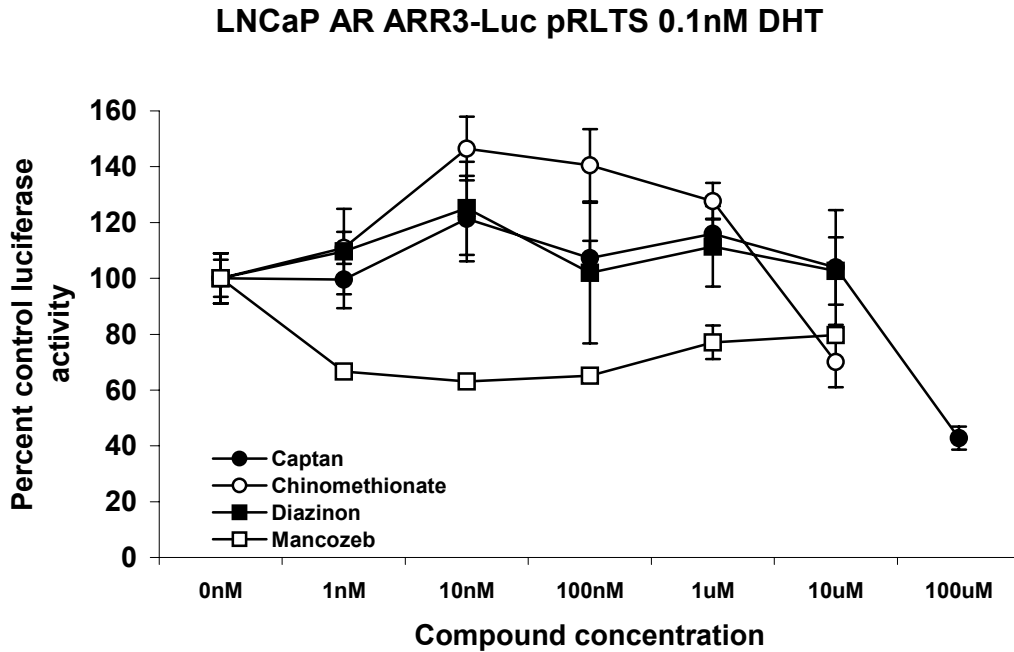
? = p<0.10; * = p<0.05; ** = p<0.01

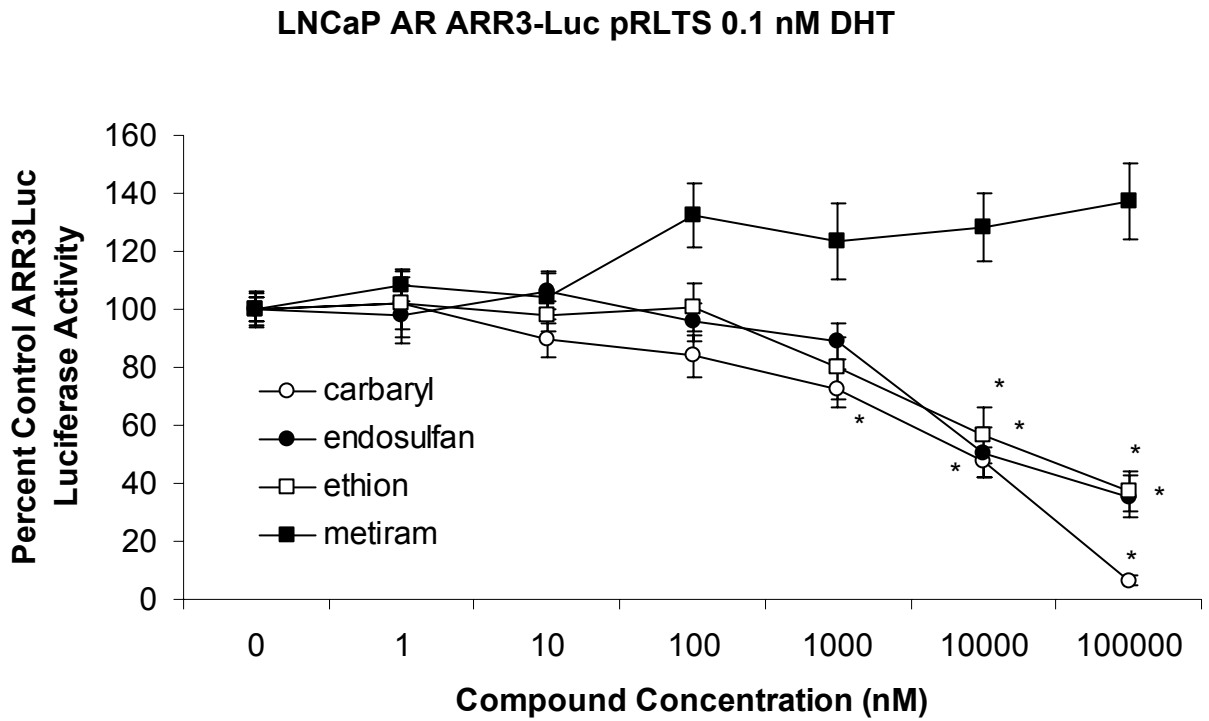
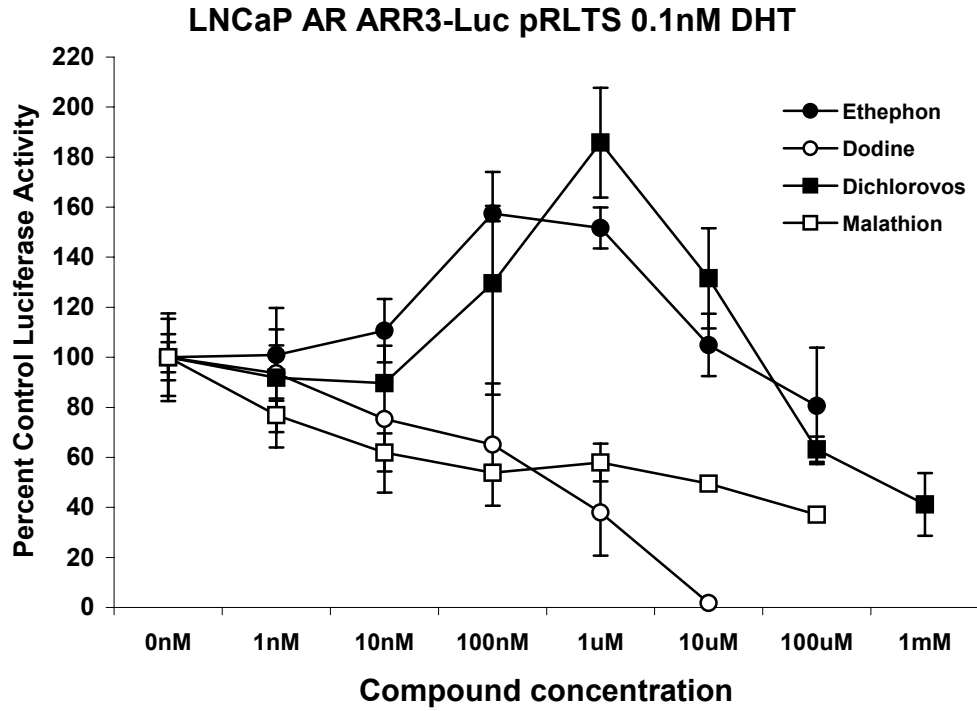
TABLE 3: Number of workers exposed (ever) to the pair of chemicals

	2,4-D	2,4 - DB	Azinphos-methyl	Captan	Carbaryl	DDT	Dichlone	Dinoseb Amine	Dodine	Ferbam	Maneb	MCPA	Simazine	Natural Gas
2,4-D	23	20		15				20				22		15
2,4 - DB	20	66	18	48	35	30	12	63	12	15	25	49	26	52
Azinphos-methyl		18	109	108	103	94	90	26	87	87	80	22	92	21
Captan	15	48	108	193	153	153	90	69	87	108	108	57	105	56
Carbaryl		35	103	153	173	146	86	48	87	107	106	38	101	40
DDT		30	94	153	146	162	81	48	79	97	102	41	95	40
Dichlone		12	90	90	86	81	90	19	86	86	70	16	77	13
Dinoseb Amine	20	63	26	69	48	48	19	88	19	22	35	66	35	60
Dodine		12	87	87	87	79	86	19	87	86	71	16	74	13
Ferbam		15	87	108	107	97	86	22	86	108	88	17	76	17
Maneb		25	80	108	106	102	70	35	71	88	108	31	76	31
MCPA	22	49	22	57	38	41	16	66	16	17	31	82	30	49
Simazine		26	92	105	101	95	77	35	74	76	76	30	106	29
Natural Gas	15	52	21	56	40	40	13	60	13	17	31	49	29	108

Figure 2. LNCaP AR / DHT Androgen Responsive Reporter Luciferase Assays

AR, ARR3-Luc, pRLTS Incubated in the presence of a range of concentrations of the compound of interest (0.1nM DHT was added).





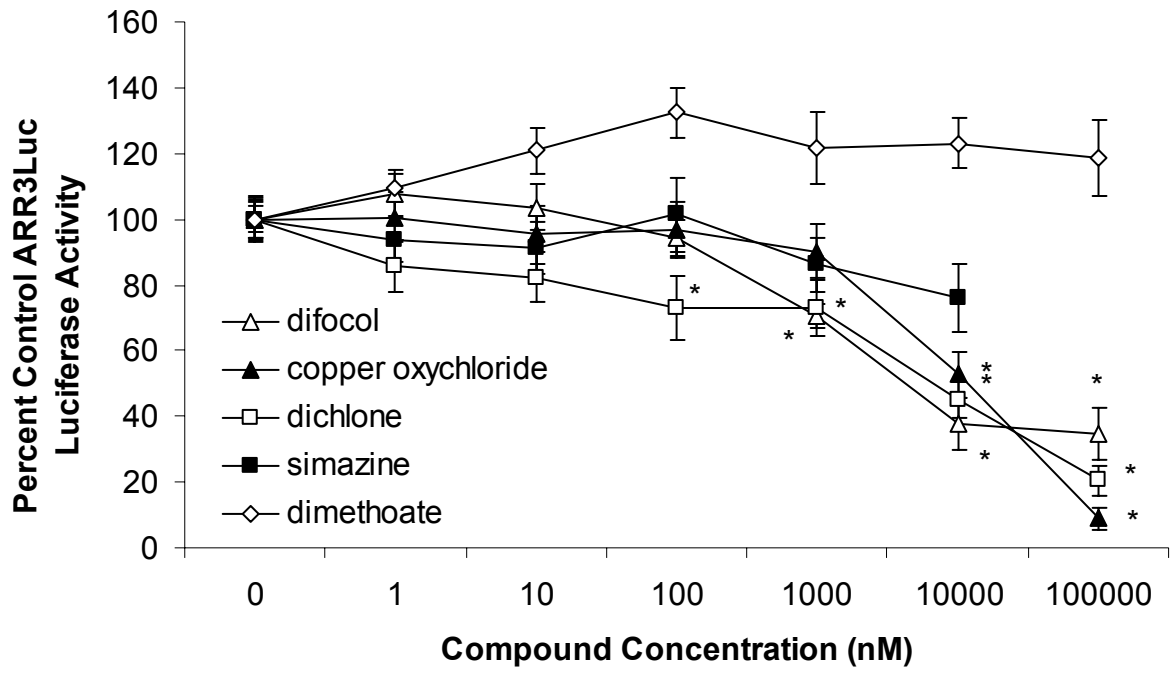
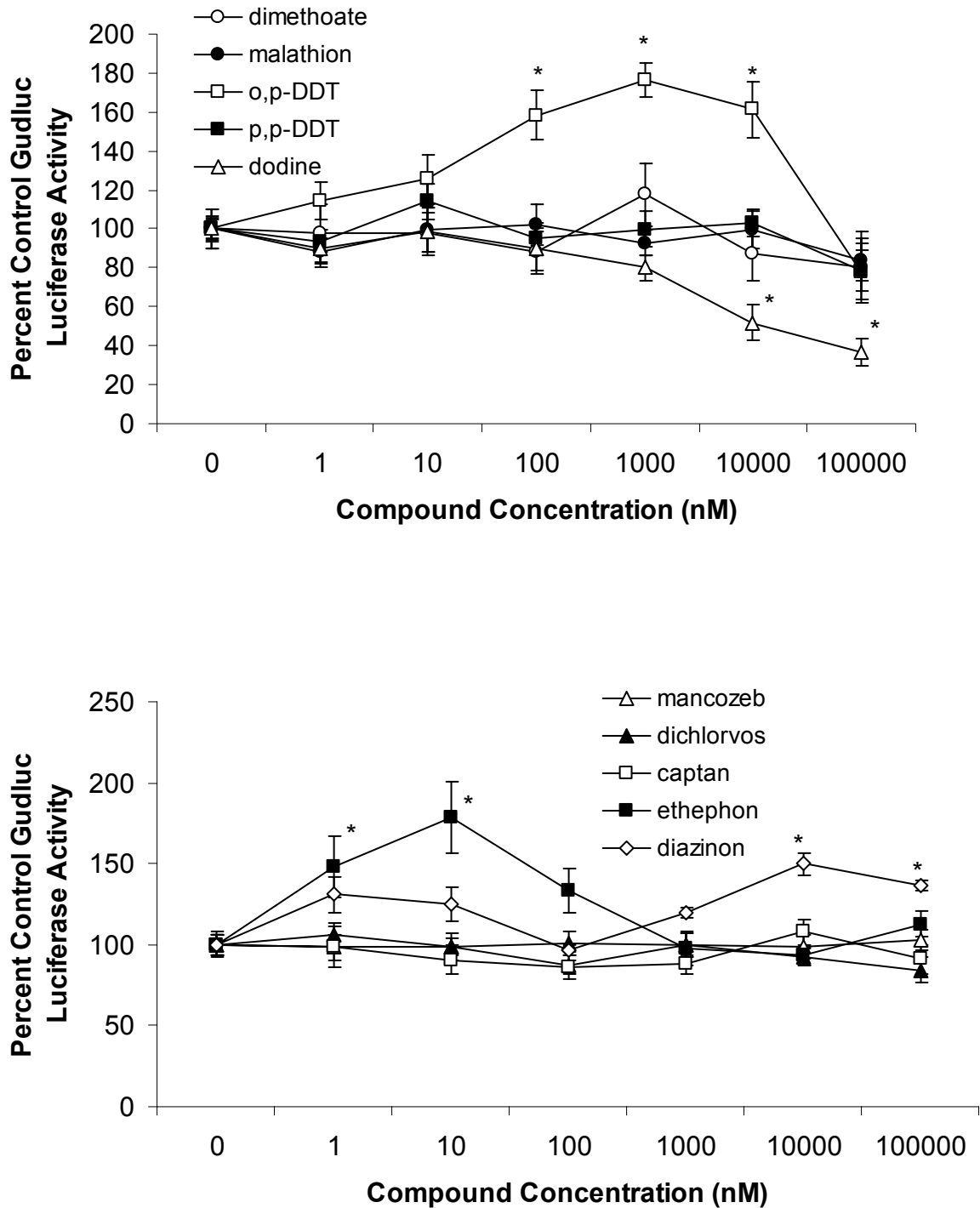


Figure 3. LNCaP Aryl Hydrocarbon Receptor Responsive Reporter Luciferase Assays

AhR Gudluc 1.1 pRLTS Incubated in the presence of a range of concentrations of the compound of interest (no TCDD was added).



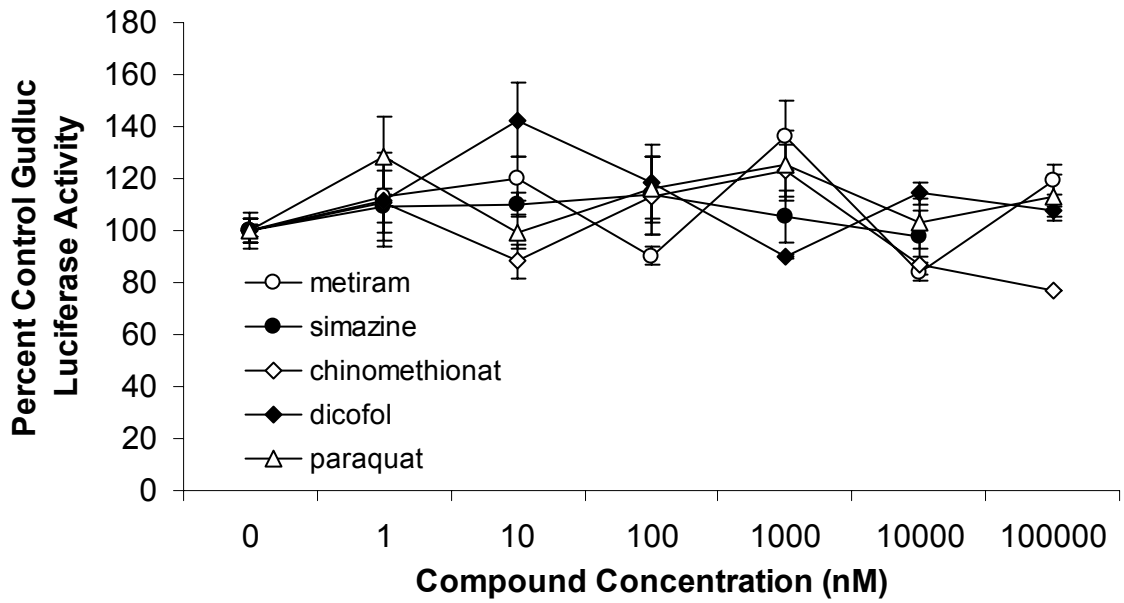
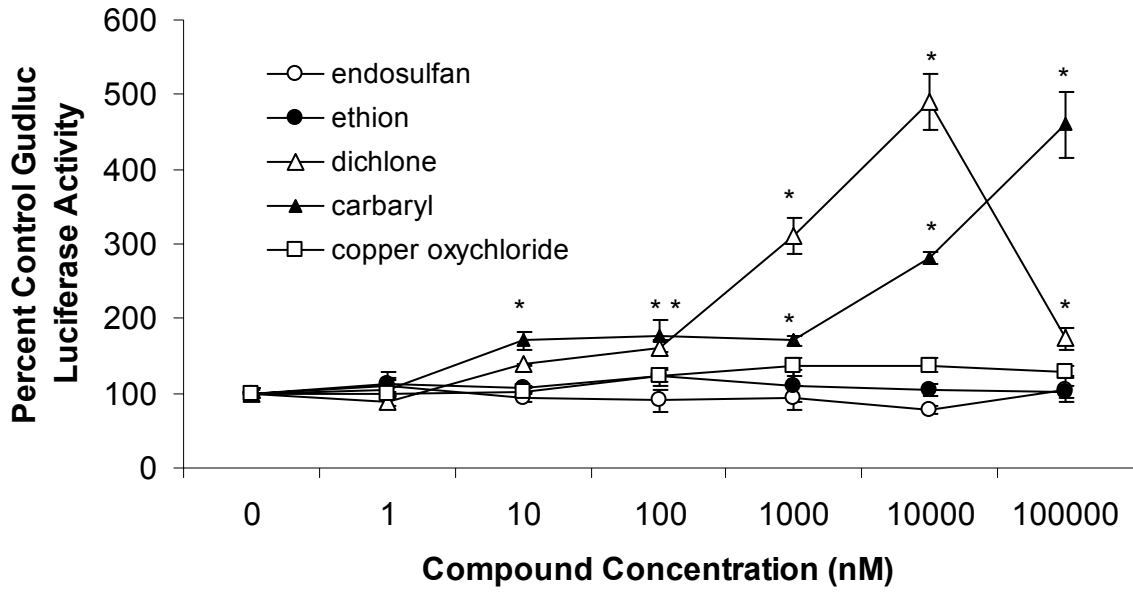
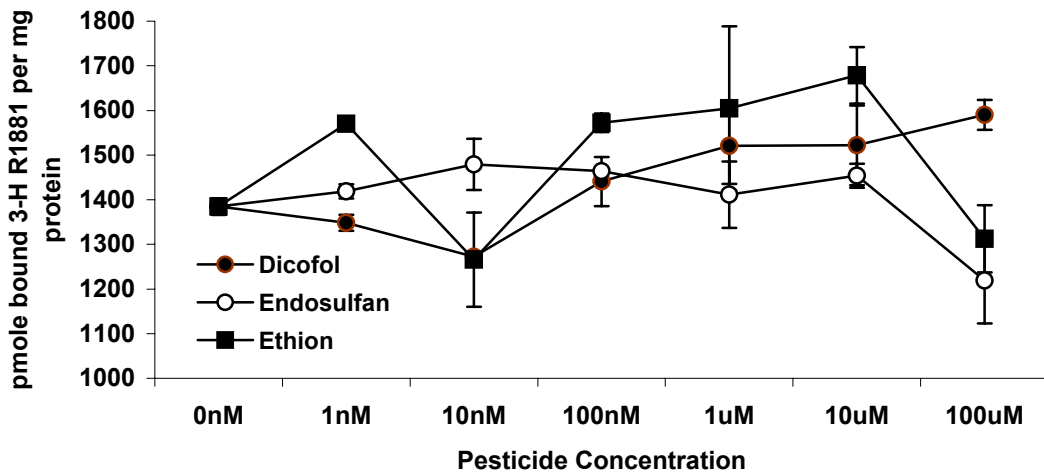
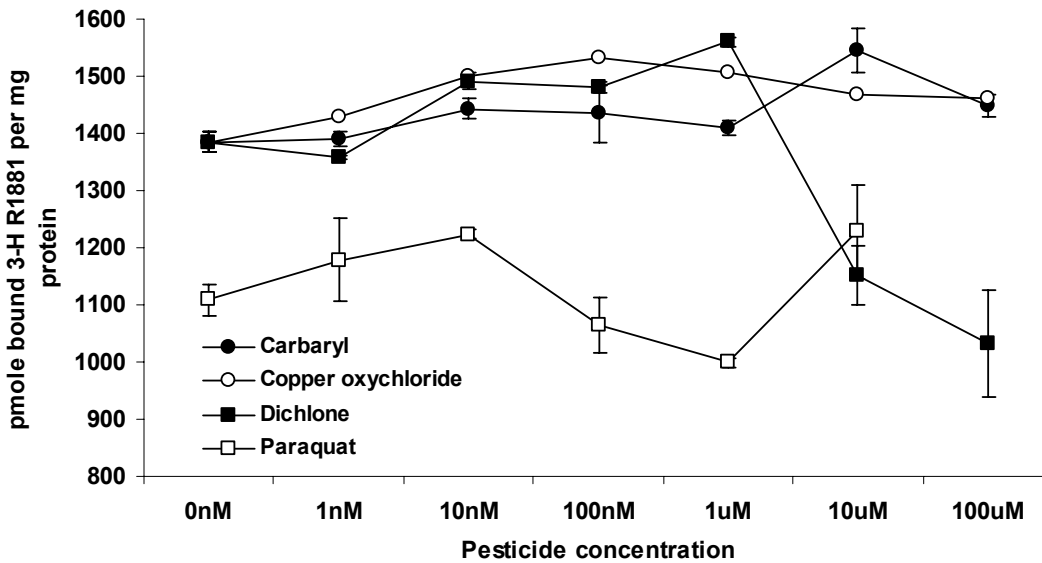
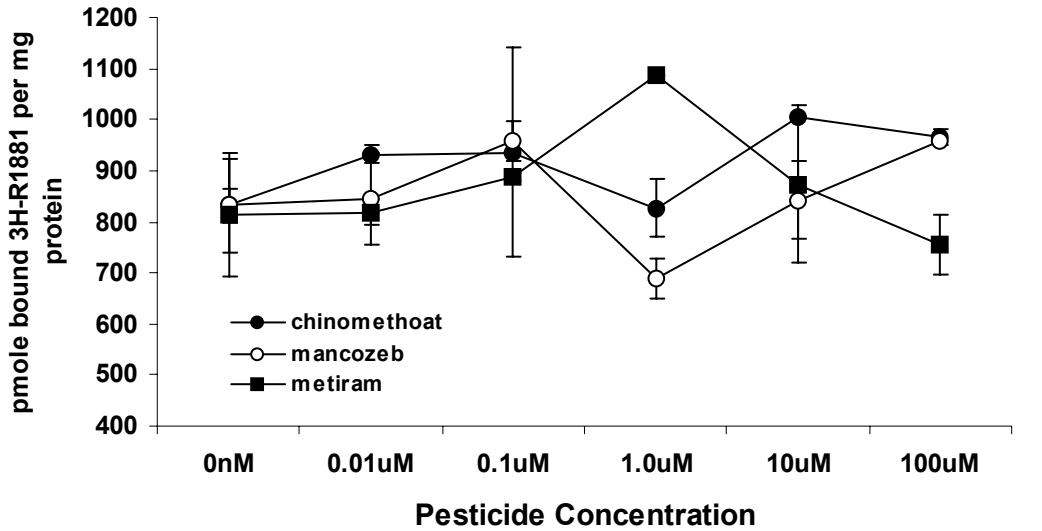
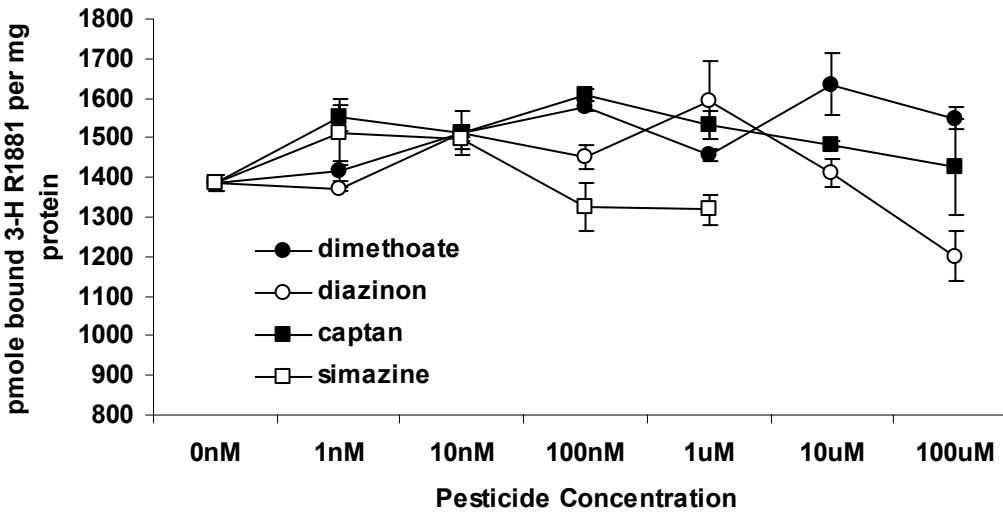
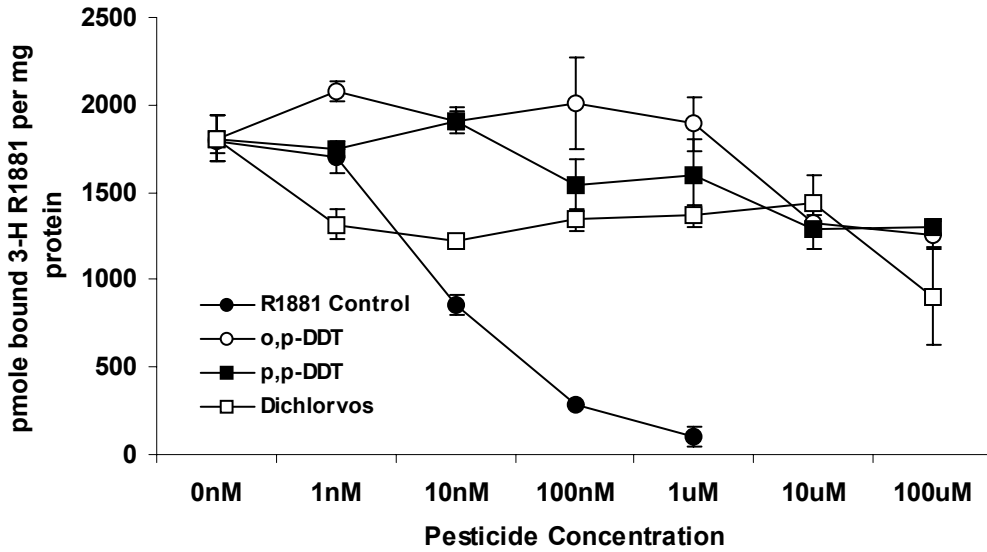
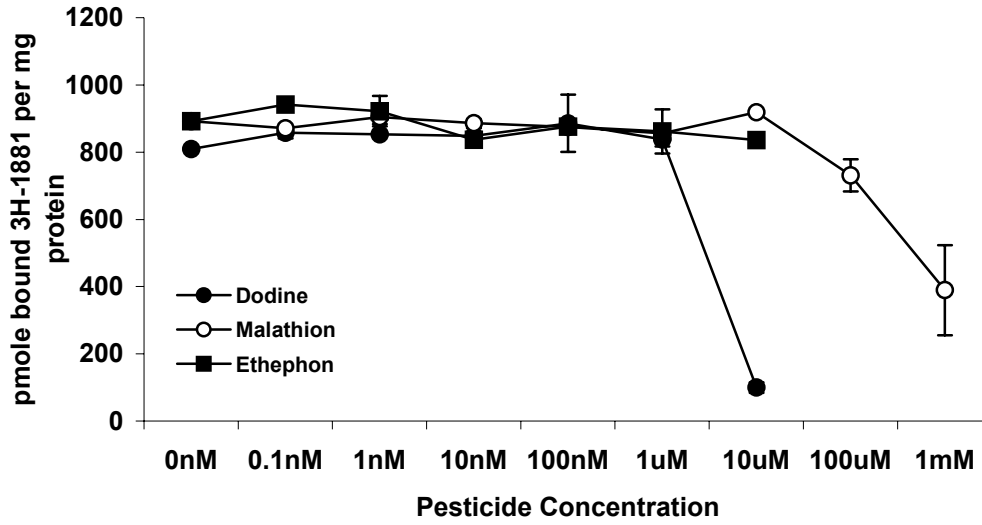


Figure 4. Androgen Receptor-Ligand Binding Domain R1881 Competitive Binding Assays





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