National Cancer Institute

Cancer Risk and Occupational Exposure to Pesticides

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Overview of Presentation on Pesticides and Cancer

- Background and rationale
- Epidemiologic studies of cancer in populations occupationally exposed to pesticides
- General versus specific chemical assessments
- Strengths and weakness of epidemiologic studies
- Future needs

Why Study Pesticides?

- Designed to do harm
- May affect many endpoints
- Some cause cancer in animals
- Make health and economic contributions
- Require societal tradeoffs
- Heavy occupational exposures
- Widespread exposures to the general population

ORGANIC PESTICIDES CAUSING CANCER IN ANIMALS ACCORDING TO IARC

Pesticide	Type	Cancer
Aldrin	I	Liver, thyroid
Amitrole	H	Liver, thyroid
Chlordane	I	Liver
2,4,6-Trichlorophenol	H	Liver
DDT	I	Liver, lung
Diallate	H	Liver, lung, lymphoma
Dicofol	I	Liver
Dieldrin	I	Liver
Ethylene dibromide	I	Liver, breast, lung
Mirex	I	Liver, lymphoma
Tetrachlorvinphos	I	Liver, thyroid
Toxaphene	I	Liver, thyroid

I = insecticide; H = herbicide

PESTICIDES WITH LIMITED EVIDENCE FOR CARCINOGENICITY IN ANIMALS ACCORDING TO IARC

Chlorabenzilate	Heptachlor	Lindane
Captan	Monuron	Arsenic acid
Carbaryl	Methyl Parathion	Chlorothalonil
Calcium arsenate	Copper arsenate	Sodium arsenate

Conclusions from Animal Bioassays

- **Only a minority test positive in at least one sex of one species (less than 25%)**
- **No clear chemical grouping of those with positive tests**

Possible Mechanisms of Action for Pesticides

- **Genotoxicity -** Not strong mutagens, less than half show mutagenic activity
- **Immunotoxicity -** Can produce hypersensitivity or immunosuppression
- **Epigenetic influences** – e.g., teleomere shortening, DNA methylation
- **Cell proliferation** – Turn over rate related to cancer
- **Peroxisome Proliferation –** Several pesticides are proliferators, but relevance to humans unclear

Studies of Cancer and Pesticides

- Studies of cancer mortality and incidence among farmers
- Studies of other groups
  - migrant workers
  - gardeners
  - pesticide manufacturers & applicators
  - golf course superintendents

Overview of Surveys of Cancer Mortality and Incidence Among Farmers

- Many publications
- Most occur since 1980
- From many countries
- Little characterization of exposure (mainly focus on farmers as a group)
- Data from death certificates, cancer registries, censuses, and national surveys

Characteristics of 46 Surveys of Cancer Among Farmers

- **Exposure characterization**
  - 32 only characterized as farmers
  - 5 by farm type
  - 5 with some pesticide indicator
  - 4 by geographic region, living on a farm
- **Cancer outcome**
  - 27 mortality; 19 incidence
- **Countries**
  - Australia, Brazil, Denmark, England/Wales, Finland, Iceland, Israel, Italy, Japan, New Zealand, Netherlands, Norway, Spain, South Korea, Sweden, Switzerland
  - Canada (countrywide and from Alberta, British Columbia, Saskatchewan)
  - United States (countrywide and from AL, CA, IA, IL, KS, MA, MO, NC, NY, WA, WI)

Findings from Meta-Analyses of Cancer Mortality and Incidence Among Farmers

Cause of Death	Blair et al (1992) #Studies	Blair et al (1992) RR	Acquavella et al (1998) #Studies	Acquavella et al (1998) RR
All causes	10	0.86*	7	0.76*
Ischemic heart disease	12	0.89*	14	0.86*
All cancer	20	0.89*	22	0.84*

Findings from Meta-Analyses of Cancer Mortality and Incidence Among Farmers

Cause of Death	Blair et al (1992) #Studies	Blair et al (1992) RR	Acquavella et al (1998) #Studies	Acquavella et al (1998) RR
Lip	8	2.08*	14	1.95*
Esophagus	18	0.74*	25	0.77*
Lung	24	0.66*	29	0.66*
Bladder	21	0.85*	29	0.79*
Skin	8	1.04	19	1.15*
Stomach	24	1.12*	29	1.05
Colon	15	0.87*	29	0.84*
Pancreas	20	0.98	28	0.94
Prostate	22	1.08*	30	1.07*
Testis	10	0.88	14	0.97
Brain	18	1.05	28	1.06*
NHL	14	1.05	23	1.03
Hodgkin disease	12	1.16*	26	1.09
Myeloma	12	1.12*	22	1.09
Leukemia	23	1.07*	27	1.10*
Connective tissue	7	1.06	6	1.06

*Statistically significant

Conclusions from of Surveys of Cancer Mortality and Incidence Among Farmers

- Results from two meta-analyses reasonably consistent
- Significant deficits for all causes, heart disease and all cancer combined
- Significant deficits for cancers of the esophagus, colon, lung, and bladder
- Significant excesses for leukemia and cancers of the lip and prostate
- Indications of excesses for NHL, myeloma, connective tissue and cancers of the skin, stomach and brain

Meta-analyses of Specific Cancers Among Farmers (mostly case-control studies)

- **Hodgkin disease – combined RR from 30 studies=1.25* (Khuder et al. SJWEH 1999;25:436)**
- **NHL – combined RR from 36 studies=1.10* (Khuder et al. SJWEH 1998;24;255-261)**
- **Leukemia – combined RR from 31 studies of pesticide-exposed population=1.21.**

  RR=1.38* for myeloid leukemia among farmers (Maele-Fabry et al. Cancer Cause Control 2007;18:457-478)
- **Brain cancer – combined RR from 33 studies=1.30* (Khuder et al. AJIM 1998;34:252-260)**
- **Multiple myeloma – combined RR from 32 studies=1.23* (Khuder & Matgi. AJIM 1997;32:510-516)**
- **Prostate cancer – combined RR from 22 studies of pesticide-exposed occupations=1.13* (Maele-Fabry & Willems. OEB 2003;60:634-642)**

Results from Selected Studies of Soft Tissue Sarcoma Among Farmers

- **Swedish farmers – RRs from four case-control studies were 2.7 and 3.3 for exposure to phenoxyacetic acids and chlorophenols**
  (Hardell et al. Int J Oncology 1995;6:847-851)
- **Canadian farmers – RR for farmers overall=1.03, for chicken farmers=1.63***
  (Hossain et al. JOEM 2007;49:1386-1393)
- **England farmers – RR for farmers, farm managers, and market gardeners=1.7***
  (Balarajan & Acheson. J Epi Com Hlth 1984;38:113-116)
- **Kansas farmers – RR=1.0, no association with pesticide use (Zahm et al. JAMA 1986;256:1141-1147)**

Results from Selected Studies of Lung Cancer Among Farmers

- **New Zealand – RR overall=0.70*.**
  0.81 for livestock, 0.66* for dairy, and 0.87 for crop farmers.
  (Reif et al. Int J Epid 1989;18:768-774)
- **Canada – more farmers among community controls than cases. No excesses with an pesticides. (McDuffie et al. JOEM 1990;32:996-1002)**
- **Italy – Overall RR=0.64*, decreased with increasing number of diary cattle (Mastrangelo et al. Am J Epid 2005;161:1037-1046)**
- **India – RR=1.92* among sugar cane workers. Excesses occurred for preparation of and burning of fields.**
  (Amre et al. OEM 1999;56:548-552)
- **Agricultural Health Study in the U.S.**
  - **RRs of 0.4* and 0.3* for applicators and spouses**
    (Blair et al. Ann Epidemiol 2005;15:279-285)
  - **Exposure-response gradients with dicamba, metolachlor, pendimethalin, carbofuran, chlorpyrifos, diazinon, and dieldrin**
    (Alavanja et al. Am J Epidemiol 2004;160:876-885)

Details from Selected Studies of Leukemia Among Farmers

- **Canadian farmers – RR=1.32 for chicken/turkey farmers** (Semenciw et al. CJPH 1994;85:208-211)
- **Canadian farmers – RR=2.0 for beef cattle farmers** (Fritschi et al. Cancer Cause Control 2002;13:563-571)
- **Hairy-cell leukemia – RR=1.5 among farmers overall, 2.8 for forage farmers, and 1.5 to 2.4 for use of insecticides, fungicides, and herbicides** (Clavel et al. SJWEH 1996;22:285-293)
- **French farmers – RR=1.33 overall and a significant association with pesticide use** (Viel & Richardson. Soc Sci Med 1993;37:771-777)

So What Do We Know About Cancer among Farmers from Epidemiologic Studies?

- Two meta-analyses of surveys of farmers provide similar results
  - consistent deficits for esophagus, colon, lung and bladder
  - consistent excesses for leukemia, lip and prostate
  - possible excesses for NHL, myeloma, connective tissue and cancers of the skin, stomach and brain
- Consistent excesses for NHL, Hodgkin disease, leukemia, myeloma, brain and prostate in meta-analyses of studies of individual cancers
- Relative risks generally small

Conclusions from Studies of Specific Cancers among Farmers

- Relatively consistent excesses for NHL, Hodgkin disease, myeloma, leukemia and cancers of the brain and prostate
- Suggestions of excesses for soft tissue sarcoma
- Consistent deficits for lung cancer among farmers as a group
- Meaning of inconsistencies and small RR
  - Variation around a no effect
  - Exposure differences
- Pesticides possibly involved, but other exposures occur

Results from Studies of Pesticide Exposed Occupations

Migrant and Seasonal Farm Workers

Cancer	Death Certificate 24 State Proportionate Mortality[a]	United Farmworkers Incidence Study[b]
Stomach	1.22 *	1.69*
Colon	0.83*	0.75
Pancreas	0.97	1.15
Lung	1.02	0.95
Lip	3.23	NA
Melanoma	0.85	1.39
Breast	0.82	0.77
Brain	0.83	1.57
Bladder	1.05	0.67
Prostate	0.98	0.93
NHL	0.80	1.02
Hodgkin disease	0.58	0.84
Multiple myeloma	0.91	0.71
Leukemia	0.96	1.59*

From: [a]Colt et al. Am J Ind Med 2001;40:604-611

[b]Mills & Kwong. Am J Ind Med 2001;40:596-603

Results from Studies of Other Pesticide Exposed Occupations

Golf Course Superintendents

Cause of death	PMR
Heart disease	1.40*
Emphysema	1.86*
All cancer	1.36*
Stomach	1.24
Colon	1.75*
Pancreas	1.28
Lung	1.17
Skin	0.66
Bladder	0.85
Prostate	2.93*
Brain	2.34*
NHL	2.37*
Multiple myeloma	0.44
Leukemia	1.62

From: Kross et al. Am J Ind Med 1996; 29:501-506

Results from Studies of Other Pesticide Exposed Occupations

Cancer	*Swedish Gardeners & Orchardists* (SIR)
All cancer	0.9
Stomach	1.2
Colon	0.6
Lung	0.6
Bladder	0.9
Melanoma	2.1
Brain	1.5
NHL	0.8
Hodgkin disease	2.1
Multiple myeloma	1.5
Leukemia	1.1

From: Littorin et al. In Arch Occup Environ Health 1993;65:163-169

Results from Studies of Other Pesticide Exposed Occupations

Mortality Among Licensed Pesticide Applicators from Florida

Cancer	Private Applicators	Commercial Applicators
All cancer	0.77*	0.83
Stomach	0.63	1.83
Colon	0.81	0.84
Lung	0.86	1.04
Skin	1.17	1.19
Bladder	0.74	0 cases
Brain	1.28	1.62
Prostate	2.56*	0.73
Lymphosarcoma	0.32	0 cases
Hodgkin disease	1.13	0.84
Leukemia	1.31	1.23

From: Fleming et al. OEM 1999;56:14-21

Review of Studies of Cancer Among Pesticide Manufacturers and Applicators

- **Meta-analysis was not performed**
- **Detailed analyses only for NHL, lung cancer and all cancer combined**
- **No significant excesses or deficits occurred for these cancers in any study**
- **All cancer – 2/21 had elevations; 3/21 deficits**
- **Lung cancer – 6/20 has elevations;**
  3/20 deficits
- **NHL – 4/15 had elevations; 1/15 deficits**

From: Burns CJ. SJWEH 2005; 31(Suppl 1):9-17

Conclusions Regarding Studies of Non-Farm Pesticide Exposed Occupations

- **Suggestion of excesses for leukemia and cancers of the brain and prostate**
- **No clear deficits across these studies**
- **Pattern not exactly like farmers**
- **Overall evidence for a cancer association less consistent and less compelling than from farmers**

Examples of Studies of Cancer and Specific Pesticides

- **Case-control studies – Non-Hodgkin Lymphoma**
- **Cohort Study - Agricultural Health Study**

Non-Hodgkin's Lymphoma and Herbicide Exposure (Kansas)

	NHL	Controls	OR	95% CI
Nonfarmer	37	286	1.0	
Farmer				
No herb.	94	457	1.3	0.8-2.0
1-5 days/yr	19	102	1.4	0.7-2.6
6-10 days/yr	6	29	1.6	0.5-4.3
11-20 days/yr	5	13	2.6	0.8-8.8
20+	7	12	6.0	1.9-19

From: Hoar SK et al. JAMA 1986;256:1141-7.

RISK OF NHL FROM 2,4-D EXPOSURE AMONG MEN FROM KANSAS AND NEBRASKA

(From Zahm et al. Epidemiology 1990;1:349-56)

Exposure Group	Cases	Controls	OR	95% CI
Never farmed	91	470	1.0	
Farmers, no 2,4-D	188	943	1.0	0.8-1.3
Farmers with 2,4-D				
1-5 days/yr	26	77	1.7	1.0-2.9
6-20 days/yr	20	50	1.9	1.0-3.4
21+ days/yr	8	10	4.7	1.6-13

RISK OF NHL IN NEBRASKA 2,4-D USERS BY TIMING OF CHANGING TO CLEAN CLOTHES AFTER HANDLING PESTICIDES

	CASES/ CONTROLS	ODDS RATIO	CONFIDENCE INTERVAL
RIGHT AWAY	6/19	1.1	0.4-3.1
AT END OF DAY	31/73	1.5	0.8-2.6
FOLLOWING DAY OR LATER	6/4	4.7	1.1-21.5

(From Zahm et al. Epidemiology 1990;1:349-56)

Agricultural Health Study: Lead Institutions and Key Investigators

National Cancer Institute –
Michael Alavanja, Laura Beane Freeman, Joseph Coble, Aaron Blair, Jay Lubin, Gabriella Andreotti, Mustafa Dosemeci, Stella Koutros, Ola Landgren, Jay Lubin, Mark Purdue, Nat Rothman, Rashmi Sinha, Shelia Zahm
National Institute of Environmental Health Sciences -
Dale Sandler, Jane Hoppin, Freya Kamel, Martha Montgomery, Tina Saldana, David Umbach
Environmental Protection Agency –
Kent Thomas, Carol Christensen, Ruth Allen
University of Iowa - Charles Lynch, Ellen Heywood, Greg Gray, Fred Gerr, Paul Romitti, Nancy Sprince
Battelle – Charles Knott, Margaret Hayslip
National Institute for Occupational Safety and Health –
Cynthia Hines, Brian Curwin, Paul Henneberger

Agricultural Health Study
Overall Design

- Prospective cohort of farmers, farmer's spouses in Iowa and North Carolina and commercial applicators in IA
- Enrolled when getting their pesticide license between 1993-97 (N=89,634)
- Cohort is linked annually to the National Death Index and state Cancer Registries
- 84 farmers and their families participated in an intensive pesticide monitoring project
- Follow-up Phase II interview in 1999 to 2003 (N=57,637)
- Follow-up Phase III interview started in 2005
- Opportunities for targeted substudies
- Website: www.aghealth.org

Agricultural Health Study

Cohort Characteristics

	Private Applicators	Spouses
Enrolled:	52,371	32,347
State:		
Iowa	31,853	21,771
North Carolina	20,518	10,576
Race:		
White	48,367	30,755
Nonwhite	1,323	538
Gender:		
Men	50,878	220
Women	1,341	32,127
Age at enrollment:		
50+	22,506	13,715
Education:		
12+ years	43,110	28,947

Agricultural Health Study
Cancer Risks from Alachlor Exposure

Quartiles for Days of Exposure

Cancer	1st Q	2nd Q	3rd Q	4th Q	P for Trend
All cancer	1.0	1.2	1.3	1.3	0.08
Colon	1.0	1.7	2.0	0.6	0.53
Rectum	1.0	0.3	1.7	0.7	0.77
Bladder	1.0	1.2	1.7	3.6	0.03
NHL	1.0	0.6	1.5	1.1	0.53
Myeloma	1.0	0.5	1.5	3.0	0.14
Leukemia	1.0	0.8	1.2	3.0	0.05

From: Lee et al. Am J Epidemiol 2004;159(4):373-380

Cancer and Specific Pesticides in the Agricultural Health Study

(See AHS Website: http://aghealth.nci.nih.gov)

- **Alachlor – excesses for leukemia and myeloma**
- **Atrazine – no associations**
- **Carbaryl – excess of melanoma, deficit of prostate cancer**
- **Carbofuran – excess for lung cancer**
- **Chlordane/ heptachlor – excess of leukemia**
- **Chlorpyrifos – excesses for lung, rectum, brain cancer**
- **Cyanazine – no associations**
- **Diazinon – excesses for leukemia and lung cancer**
- **Dicamba – excesses with colon and lung cancer**

Cancers Associated with Specific Pesticides in the Agricultural Health Study: Continued

(See AHS Website: http://aghealth.nci.nih.gov)

- **Dichlorvos – no associations**
- **Dieldrin – excess of lung cancer**
- **Fonofos – excess of leukemia**
- **Glyphosate – excess for myeloma**
- **Lindane – excess of NHL**
- **Malathion – deficit for melanoma**
- **Metolachlor – deficit for prostate cancer, excess for lung**
- **Pendimethalin – excess for rectal cancer**
- **Phorate – excess of prostate cancer (only among those with a family history)**

Summary of Epidemiologic Studies on Cancer and Pesticides

- Excesses for cancers of the brain, prostate, soft tissue sarcoma and lymphatic and hematopoietic system in pesticide exposed populations
- Relative risks rarely large
- A few studies report associations between specific pesticides and specific cancers, but evidence limited
- Relatively small elevated risks could indicate:
  - associations do to chance or bias
  - impact of risk factors relatively weak
  - larger impact, but exposure misclassification reduces risk estimates

What Are the Major Limitations of Epidemiologic Studies of Cancer and Pesticides

- **Confounding by:**
  - **Other workplace exposures**
  - **Lifestyle factors**
  - **Genes**
- **Exposure misclassification**
  - **Differential, i.e., case-response bias**
  - **Nondifferential, i.e., the same for cancer cases as for noncases**

Confounding

- **Requirements for confounding:**
  - **Confounder must be related to the disease and as strong or stronger than the exposure of interest**
  - **Confounder must be tightly tied to the exposure of interest**
- **No information available in the study on the confounder**
- **Effects of confounder must make sense across various diseases studied**

Impact of Pesticide Exposure Misclassification

- Can be differential and/or nondifferential in case-control studies
- Largely nondifferential in cohort studies
- A little misclassification can have a big effect

Exposure and Disease Misclassification: Bias towards the Null

True Exposure Classification

	Exposed: Yes	Exposed: No	
Case	150	350	500
Control	50	450	500
	200	800	

With 20% Non-differential Misclassification of Exposure

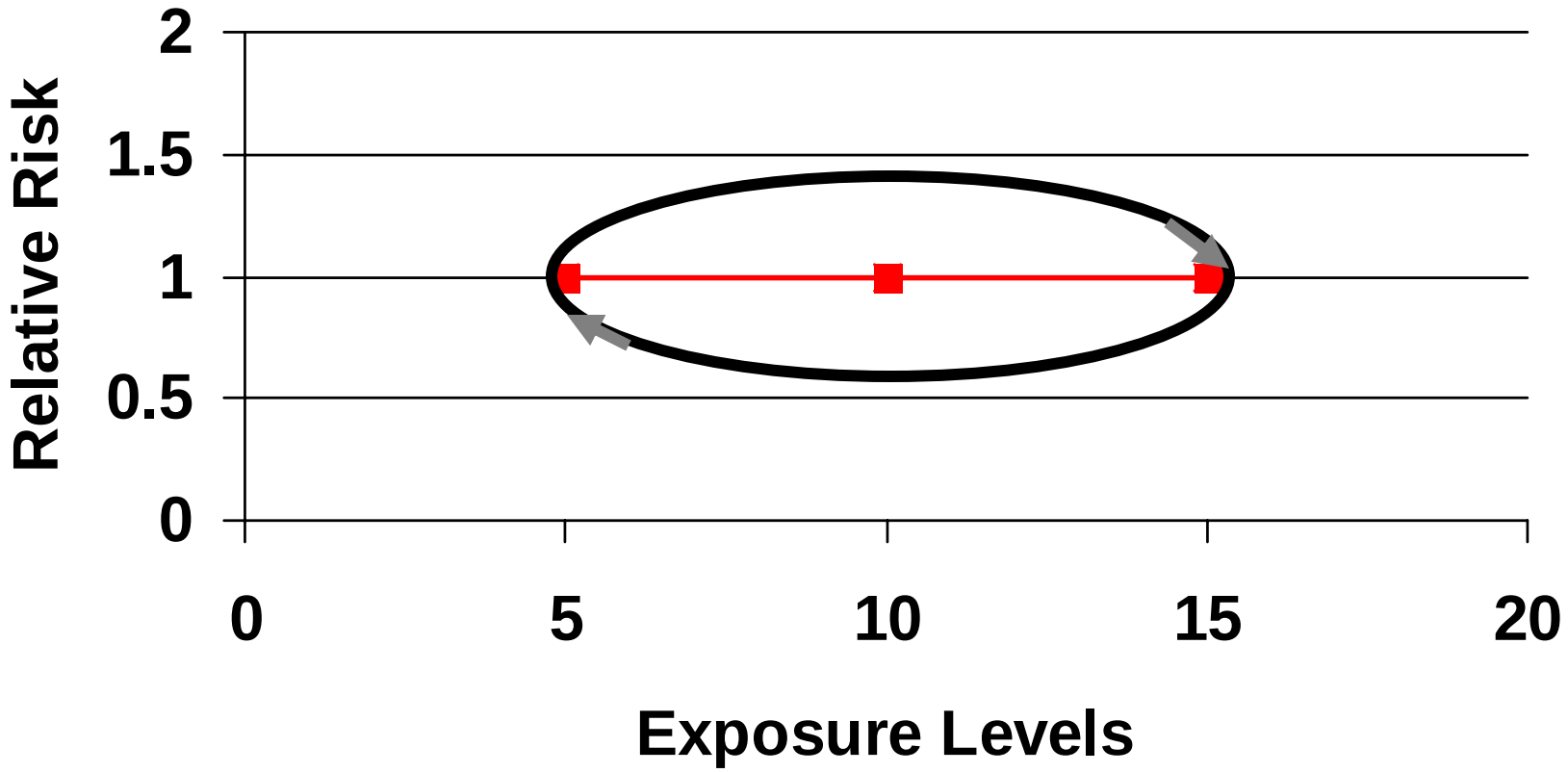
	Exposed: Yes	Exposed: No	
Case	190	310	500
Control	130	370	500
	320	680	

OR=3.9 ⟶ OR=1.7

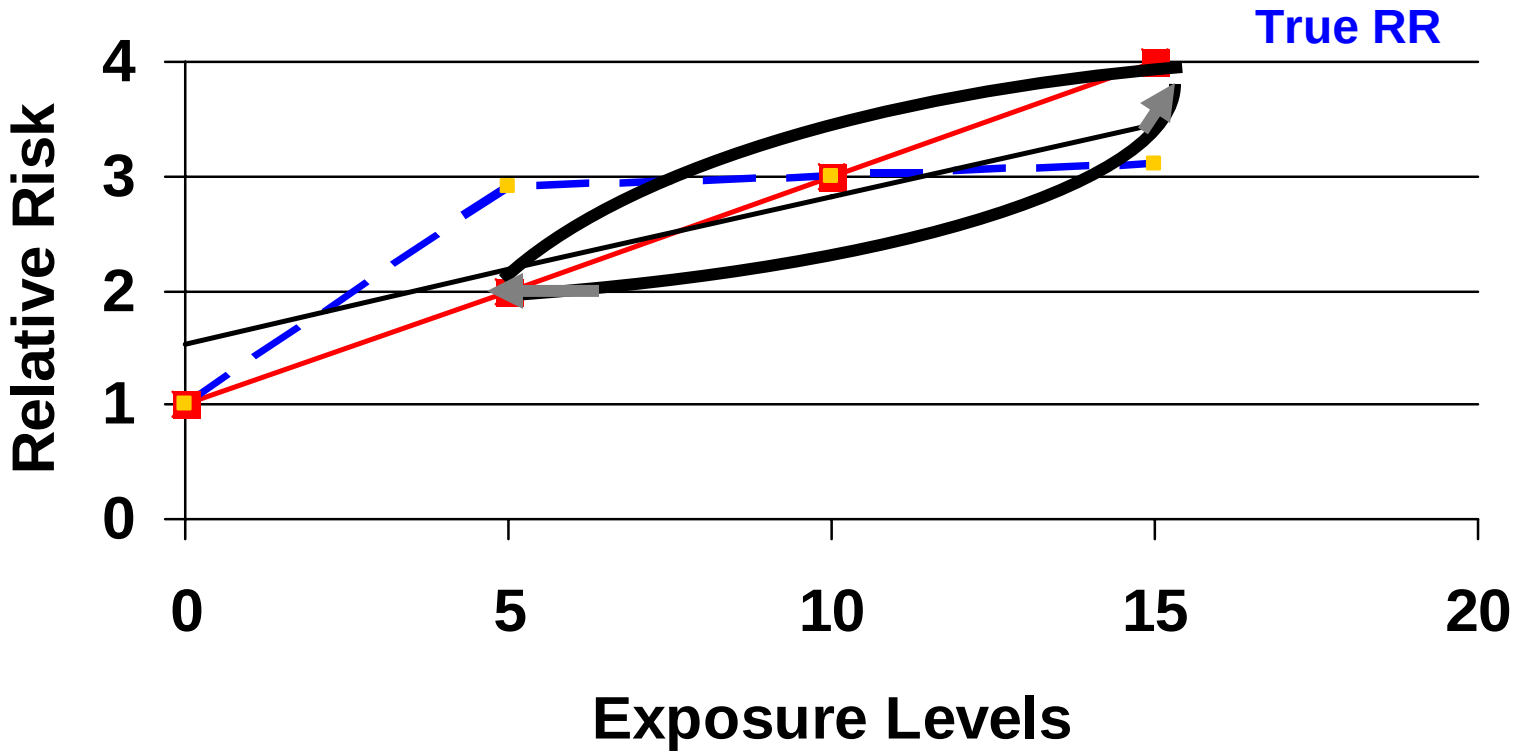
IMPLICATION - The true OR is reduced by 56% when only 20% of exposed cases and controls are misclassified.

Misclassification of Exposure: True Association

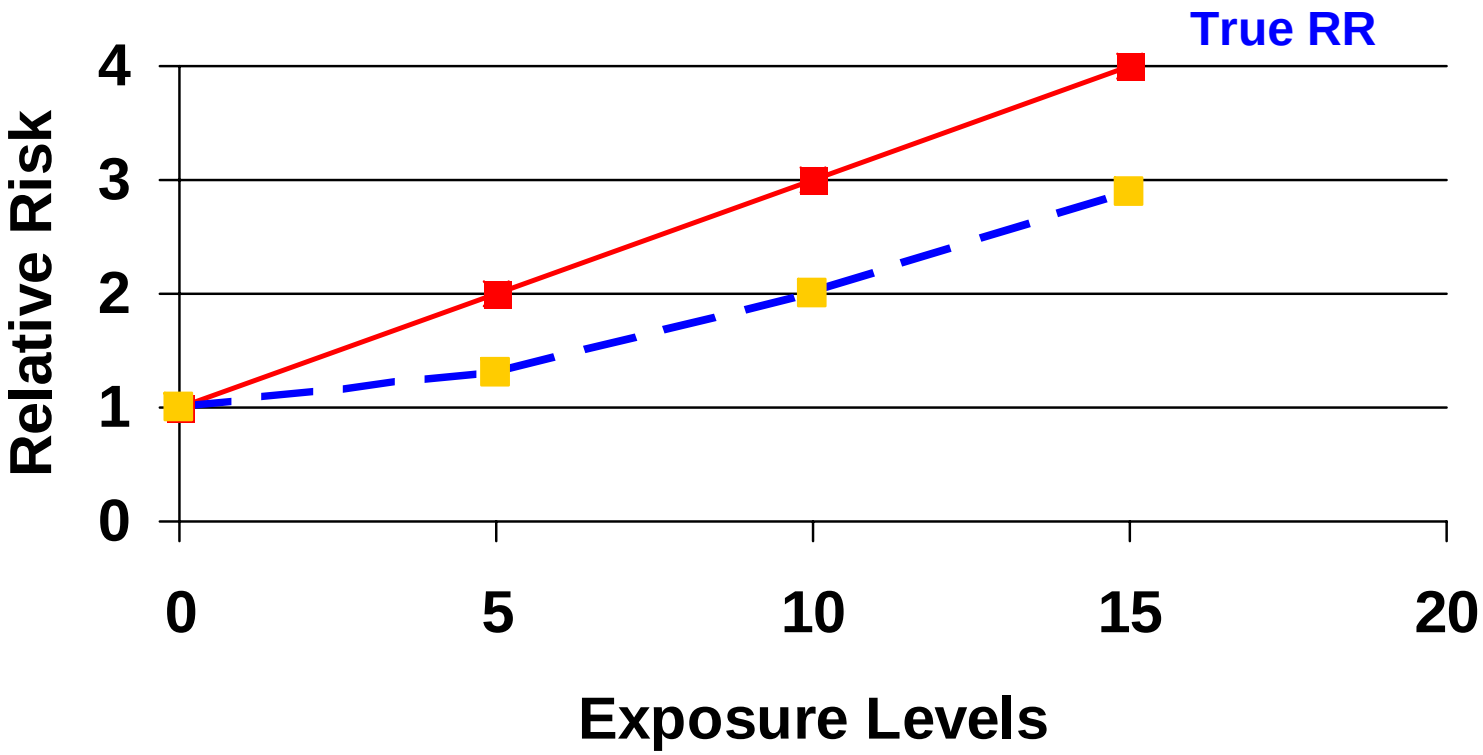
with nondifferential misclassification



Misclassification of Exposure: True Association



Misclassification of Exposure: True Association



Why is Pesticide Exposure Assessment Difficult?

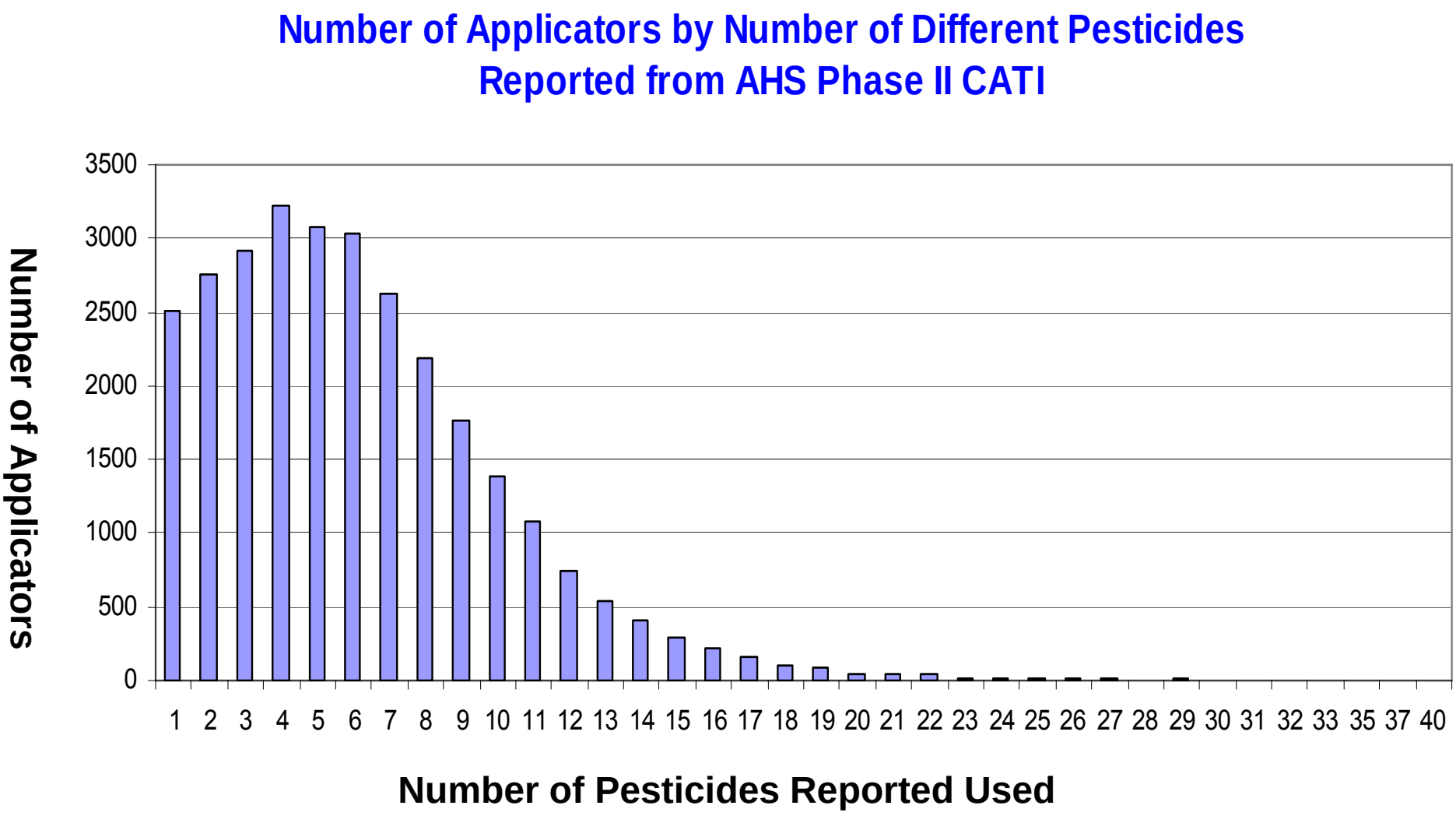
- Critical exposure probably occurs years before the development of cancer
- Delivered dose to the target tissue is the critical exposure, but never available
- Some measurements (air, dust, urine) might be available for a few recent years
- Exposure determinants can be used to estimate exposures in years past
- Determinants become more difficult to identify as time passes and this introduces error

Agricultural Health Study
Reported Exposures from Non-Farm Jobs

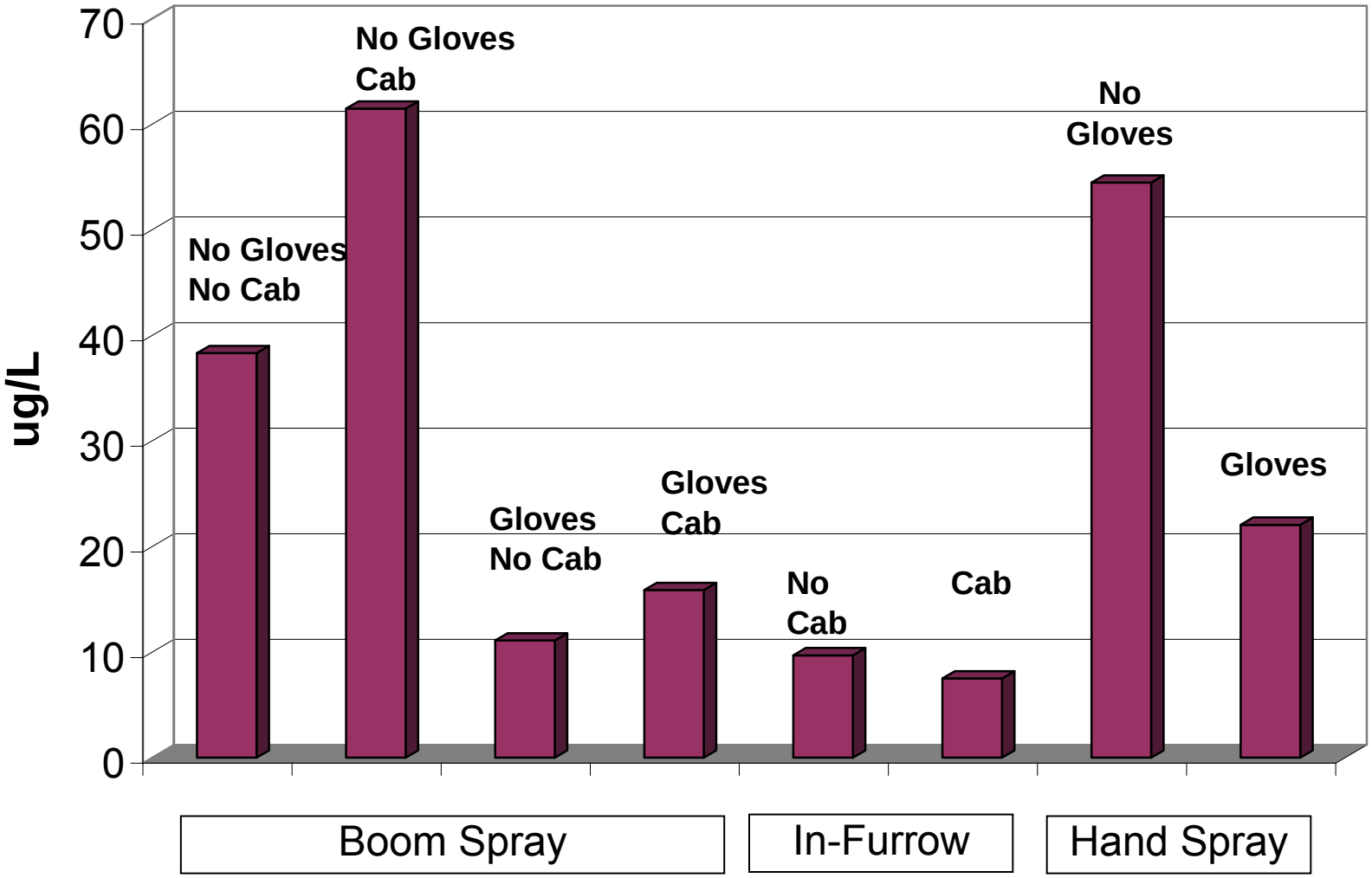
Agent	North Carolina	Iowa
Pesticides	7%	7%
Engine exhausts	20	21
Solvents	16	16
Welding fumes	16	16
Wood dust	14	8
Grain dust	4	10
Silica	5	4
Asbestos	8	4

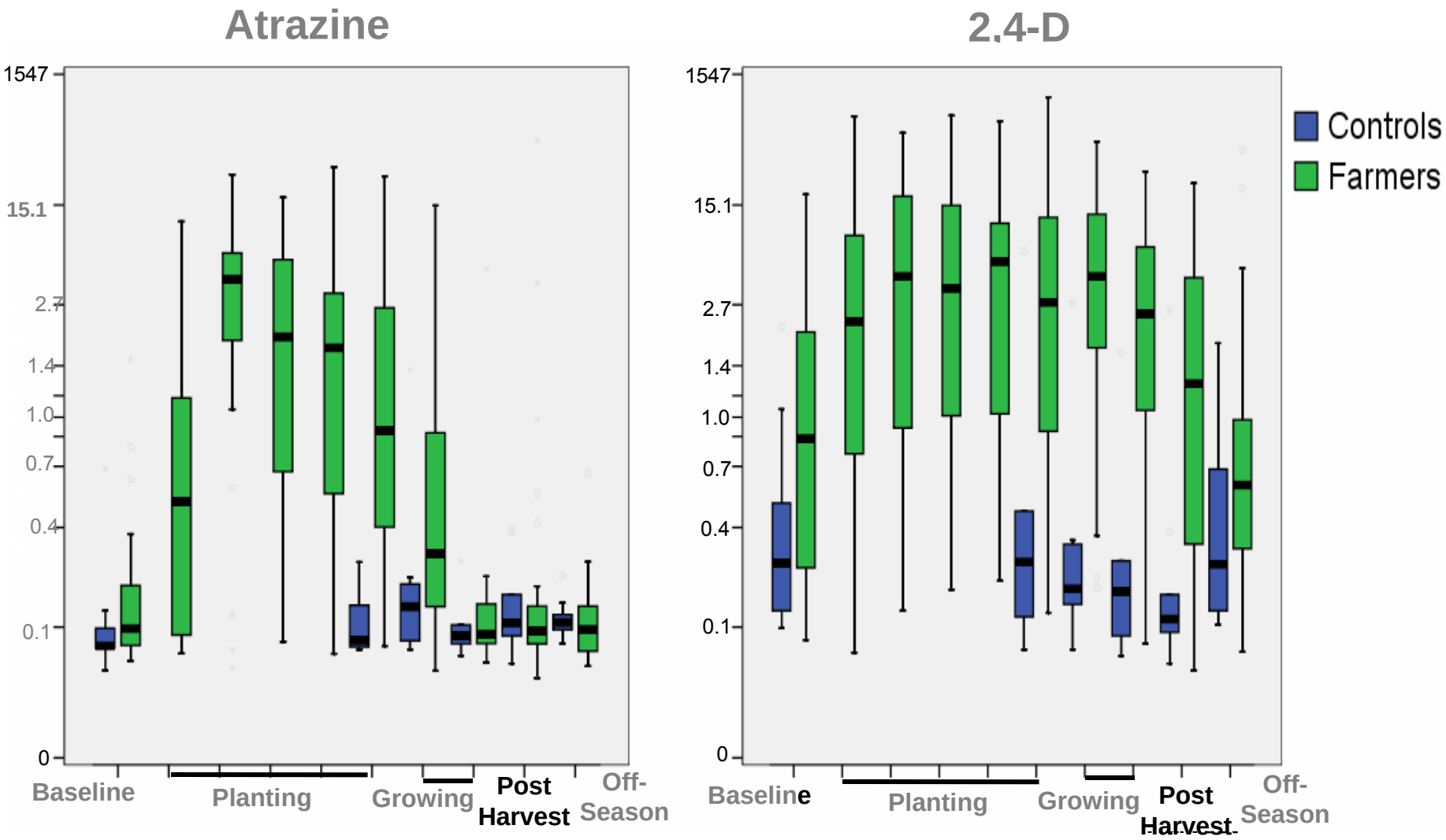
From: Coble J et al. J Exposure Anal Environ Epid 12:418-426, 2002

Number of Pesticides Per Applicator, AHS 1999 - 2003



CONCENTRATIONS IN POST-APPLICATION URINE - GEOMETRIC MEAN (ug/L)





Bakke B et al. J Exposure Sci Environ Epid (In press)

Pesticide Misclassification: Correlations between Estimates and Measurements

(From Acquavella et al. Epidemiology 2006;17:69-74)

Estimate Source	2,4-D (liquid)	Chlorpyrifos (liquid)	Glyphosate (liquid)
Qx – Self Reports	0.25*	0.42*	0.23*
Field Observation	0.45*	0.42*	0.47*

Observed Relative Risks Based on Sensitivity, Specificity, Exposure Prevalence and True Risks

True RR and Exposure Prev.	Sensitivity=0.7 Specificity=1.0	Sensitivity=0.7 Specificity=0.7
True RR = 2.0		
Exposure prev.= 10%	1.94	1.15
= 30%	1.80	1.30
= 50%	1.63	1.31
True RR = 3.0		
Exposure prev.= 10%	2.82	1.29
= 30%	2.44	1.53
= 50%	2.05	1.50

Conclusions

- Farmers probably experience excesses for some cancers and clearly experience deficits for others
- Evidence from other pesticide exposed occupations is more limited
- Literature on specific pesticide exposures is limited, but suggests cancer links with some pesticides
- Future studies should include enhanced exposure assessment and focus on specific pesticides

Thanks

Questions?