Cancer in Agricultural Populations

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NIH NATIONAL CANCER INSTITUTE

Background: Agriculture and Cancer

- Although farming is declining worldwide, it remains an important industry
- Farmers healthier than general population
  - Lower incidence:
    - Lung, bladder, colon
  - Higher incidence:
    - Leukemia, multiple myeloma, NHL
    - Lip
    - Stomach
    - Skin
    - Brain
    - Prostate cancers

Blair and Beane Freeman, J Agromedicine, 2009

Background: Agriculture and Cancer

- Numerous exposures
  - Pesticides
  - Animals
  - Diesel engine exhaust
  - Biologically active dusts
  - Zoonotic microbes
  - Fuels, oils, and solvents

- Low rates of tobacco and alcohol use
- High rates of physical activity

The Agricultural Health Study

- Designed to study a wide range of health effects of agricultural exposures in farmers and their families
- Prospective cohort of 52,000 licensed pesticide applicators and 32,000 farm spouses
  - 1993-97
- Completed questionnaires on medical history, pesticide use, and current farming
- 84% of licensed applicators enrolled

Agricultural Health Study

- Two agricultural states:

Agricultural Health Study

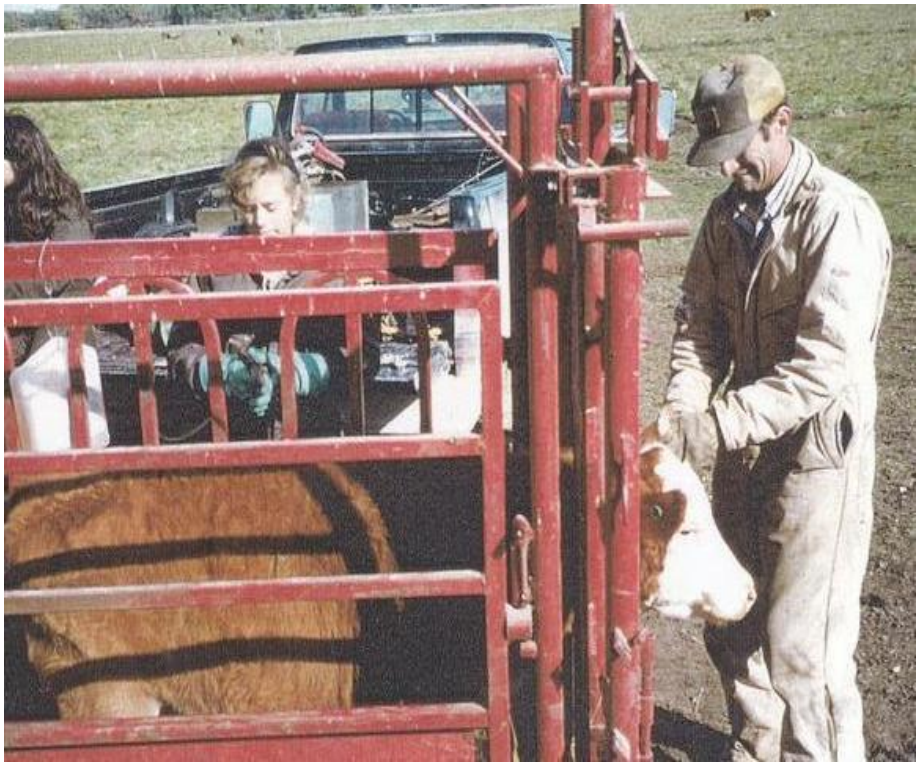
- Regular linkage to state cancer registries
  - Population-based
- National mortality registry
- 17+ years of follow-up (median age=65 years)
- >10,000 incident cancers
- Able to control statistically for use of other pesticides and other exposures

Pesticides: A Worldwide Exposure

- 2.4 billion kg pesticide active ingredients applied worldwide in 2007
- 500 million kg of pesticide active ingredients used in 1993 in the USA
  - 890 different active ingredients
- World-wide over 1 billion people occupationally exposed to pesticides

Pesticide Application Methods: Field Crops

Pesticide Application Methods: Animals



Pesticide Application Methods: Orchards

Pesticide Application Methods: Field Crops

Mixing pesticides

Selected Pesticide Findings: Farmers

Organophosphate Insecticides

Organochlorine Insecticides

- Lindane, DDT

Chloroacetilinide Herbicides

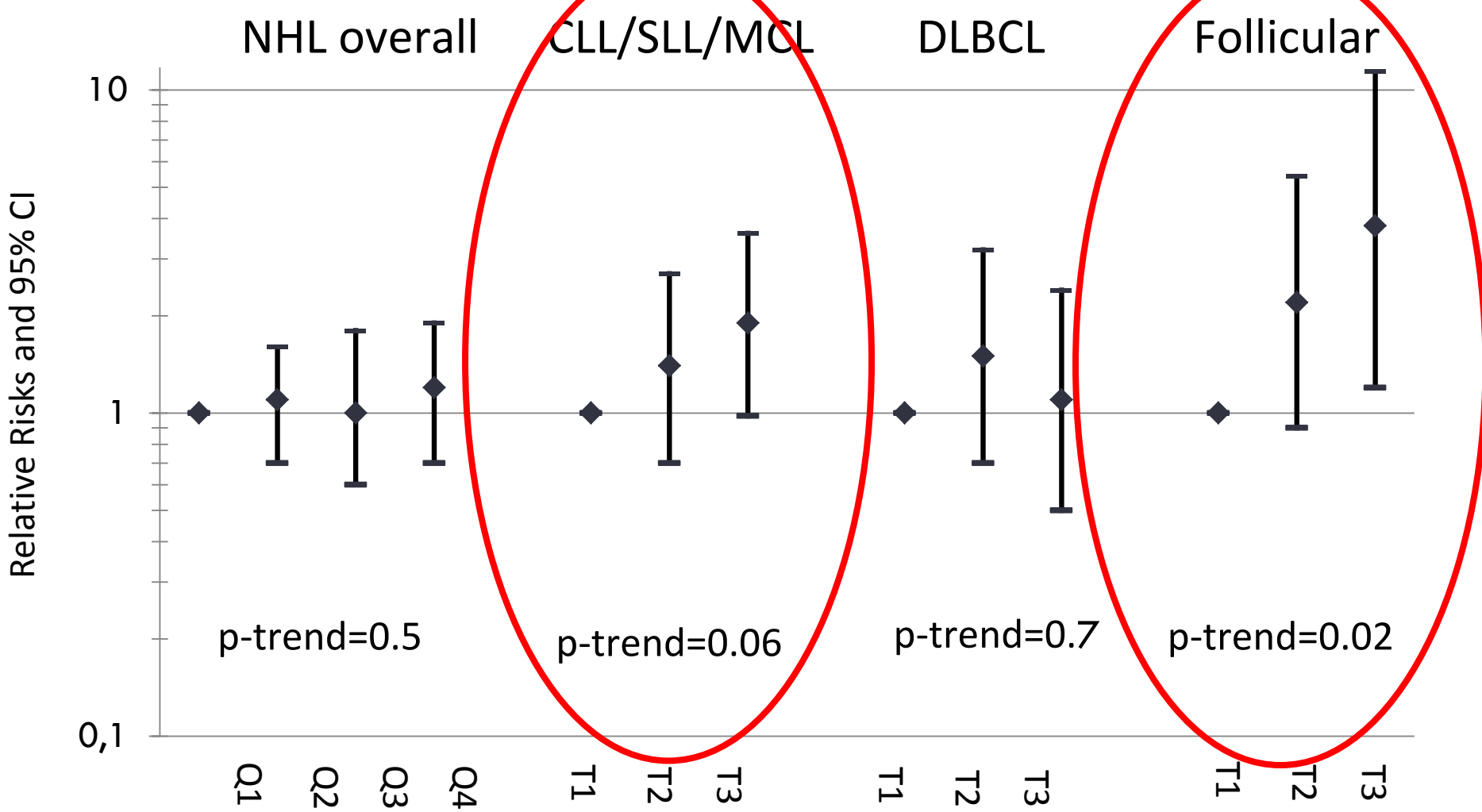
- Metolachlor
- Acetochlor

Organophosphate Insecticides

- Introduced in the 1970s
- Widespread use on crops and animals, agricultural and residential use (historically)
- Acetylcholinesterase inhibition



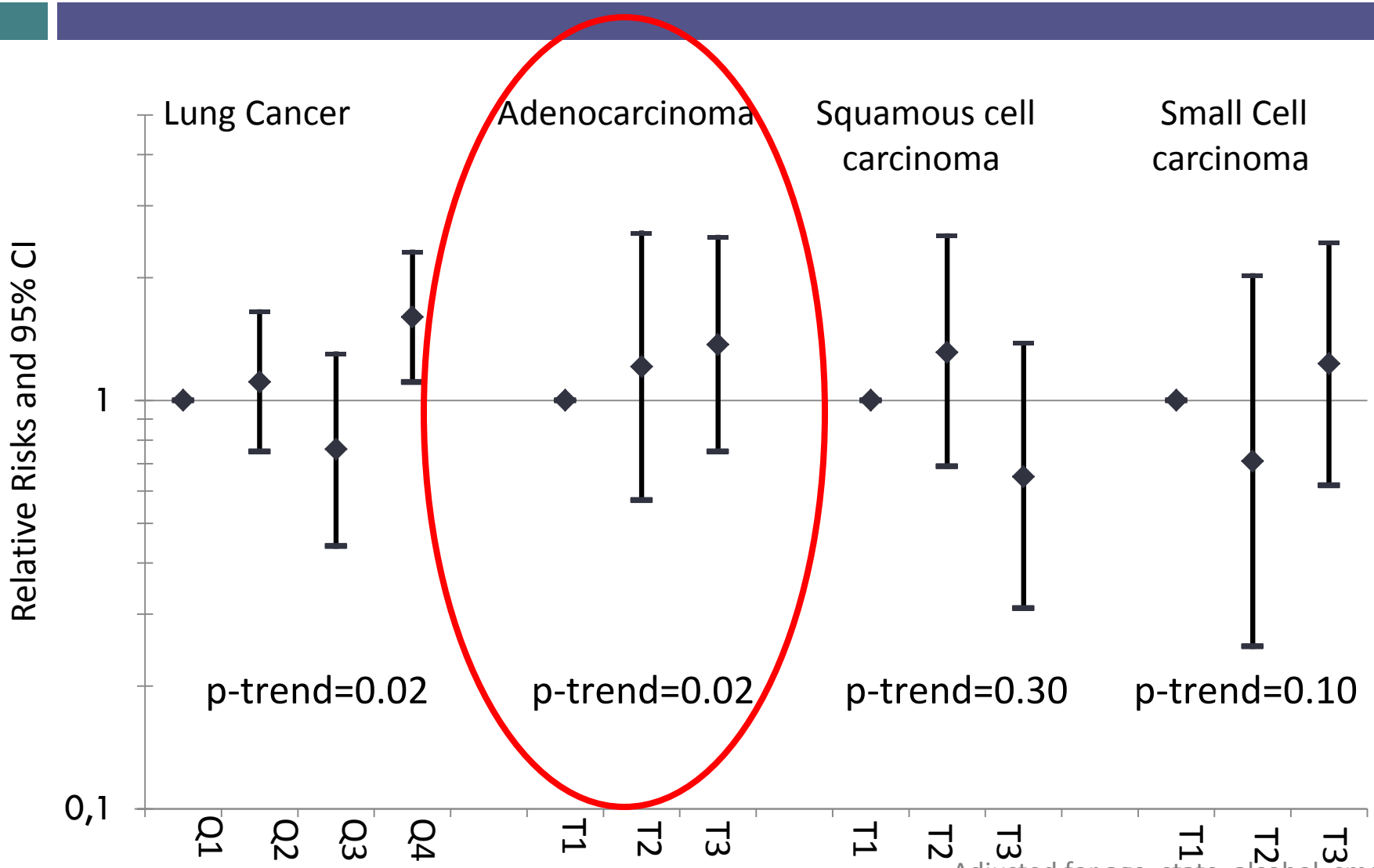

Diazinon and NHL



Adjusted for age, state, race, herbicide use

Alavanja…Beane Freeman, PLoS One 2014

Diazinon and Lung Cancer



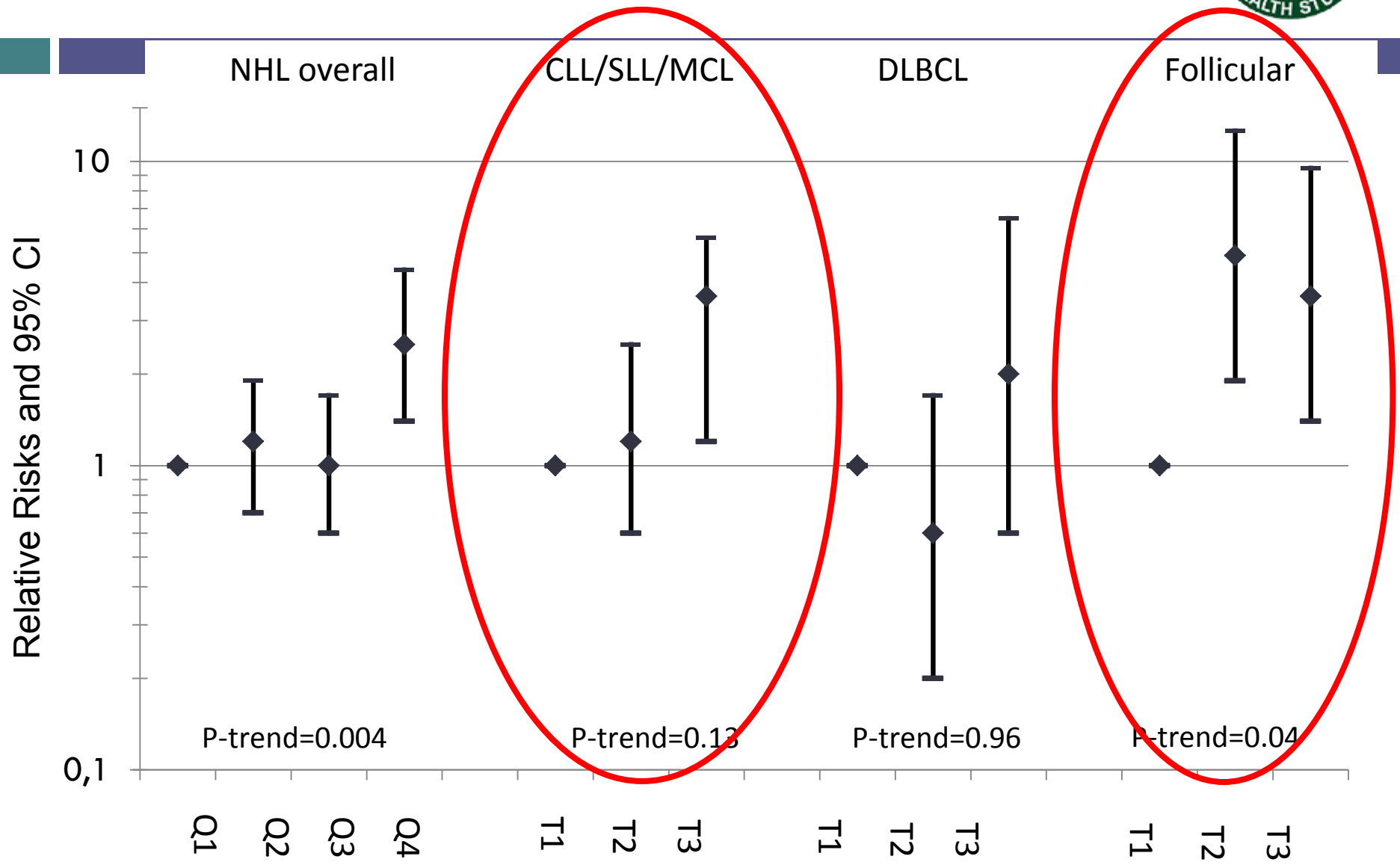
Jones…Beane Freeman, Occup Environ Med, 2015

Adjusted for age, state, alcohol, smoking, family history of cancer, education

Organochlorine Insecticides

- Introduced in the 1940s
- Persistent
- Most banned in US in 1970s
  - Lindane still used until 2006
- Many still used in around the world for vector control

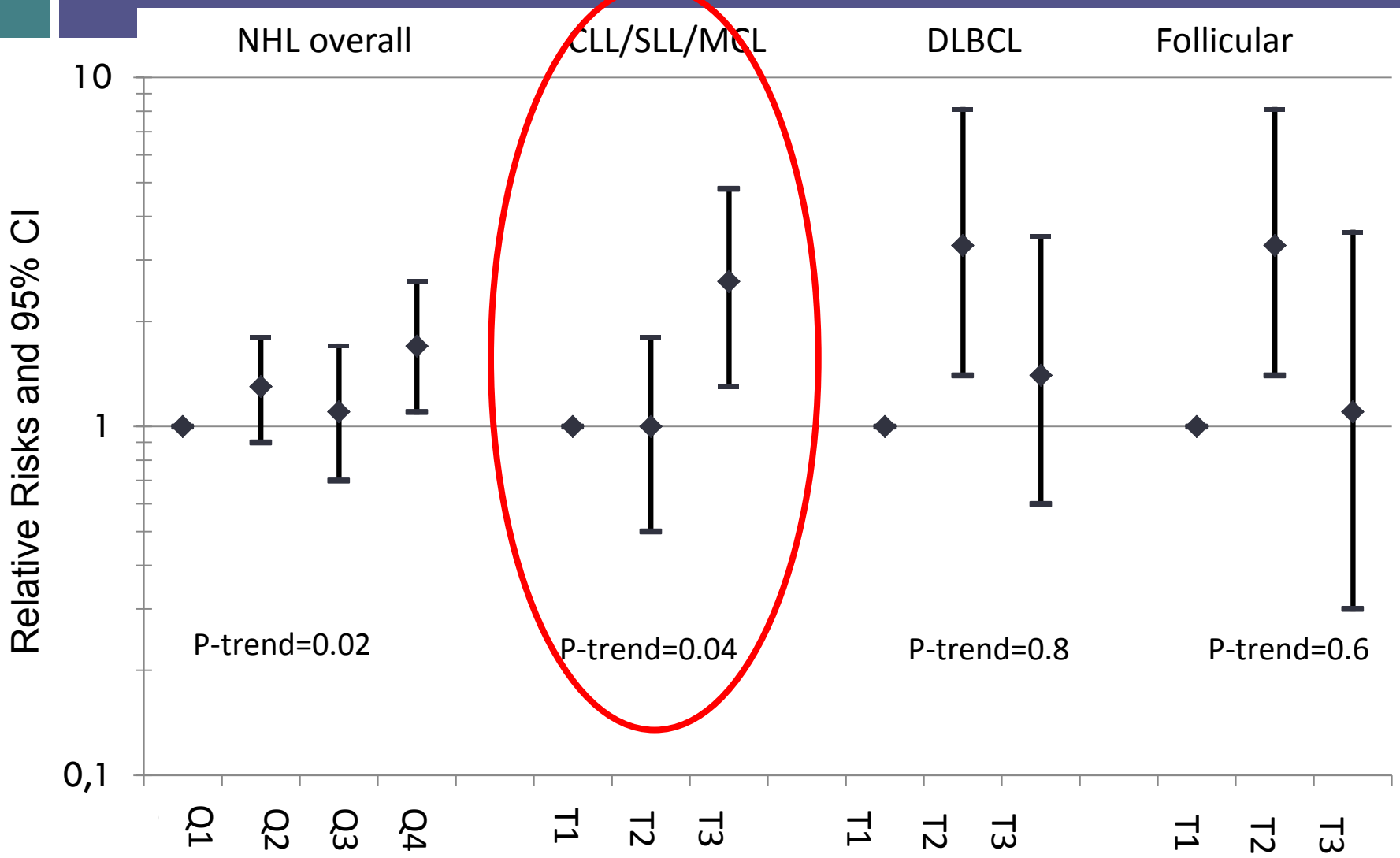
Lindane and NHL



Alavanja…Beane Freeman, PLoS One, 2014

Adjusted for age, state, race, herbicide use

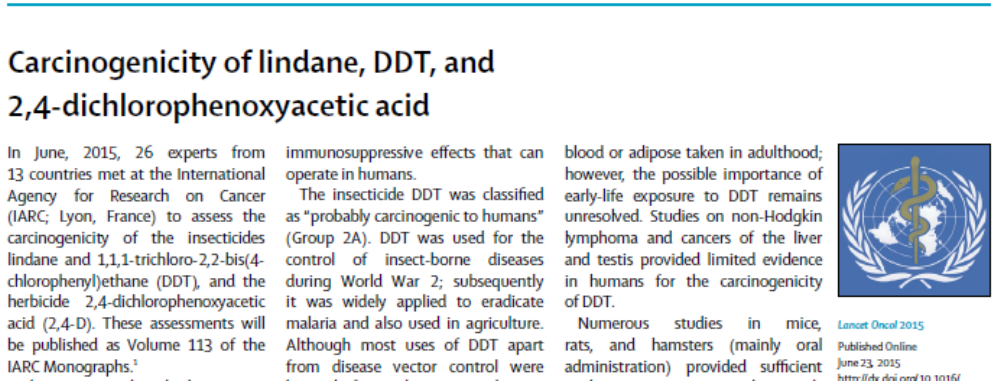
DDT and NHL



Alavanja…Beane Freeman, PLoS One, 2014

Adjusted for age, state, race, herbicide use

Recent IARC Evaluations of Pesticides



Carcinogenicity of lindane, DDT, and 2,4-dichlorophenoxyacetic acid

In June, 2015, 26 experts from 13 countries met at the International Agency for Research on Cancer (IARC; Lyon, France) to assess the carcinogenicity of the insecticides lindane and 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (DDT), and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D). These assessments will be published as Volume 113 of the IARC Monographs.[1]

immunosuppressive effects that can operate in humans.

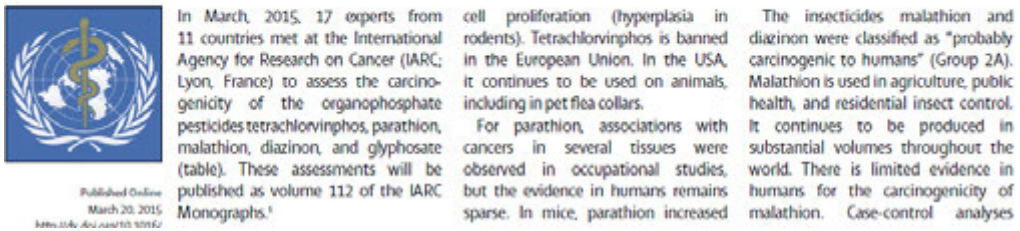
The insecticide DDT was classified as "probably carcinogenic to humans" (Group 2A). DDT was used for the control of insect-borne diseases during World War 2; subsequently it was widely applied to eradicate malaria and also used in agriculture. Although most uses of DDT apart from disease vector control were

blood or adipose taken in adulthood; however, the possible importance of early-life exposure to DDT remains unresolved. Studies on non-Hodgkin lymphoma and cancers of the liver and testis provided limited evidence in humans for the carcinogenicity of DDT.

Numerous studies in mice, rats, and hamsters (mainly oral administration) provided sufficient

Lancet Oncol 2015
Published Online
June 23, 2015

Lancet Oncol. 2015 Jun 22. pii: S1470-2045(15)00081-9.



Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate

In March, 2015, 17 experts from 11 countries met at the International Agency for Research on Cancer (IARC; Lyon, France) to assess the carcinogenicity of the organophosphate pesticides tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate (table). These assessments will be published as volume 112 of the IARC Monographs.[1]

cell proliferation (hyperplasia in rodents). Tetrachlorvinphos is banned in the European Union. In the USA, it continues to be used on animals, including in pet flea collars.

For parathion, associations with cancers in several tissues were observed in occupational studies, but the evidence in humans remains sparse. In mice, parathion increased

The insecticides malathion and diazinon were classified as "probably carcinogenic to humans" (Group 2A). Malathion is used in agriculture, public health, and residential insect control. It continues to be produced in substantial volumes throughout the world. There is limited evidence in humans for the carcinogenicity of malathion. Case-control analyses

Published Online
March 20, 2015

Lancet Oncol. 2015 May;16(5):490-1.

- These results played an important role in recent IARC monograph evaluations
  - Lindane—Group 1 (NHL)
  - DDT—Group 2A (NHL)
  - Diazinon—Group 2A (NHL and lung cancer)

Organophosphate Insecticides and Aggressive Prostate Cancer

Organophosphate Insecticide	Q4 vs. Non-exposed RR 95 % CI	P-trend
Chlorpyrifos	1.01 (0.80, 1.28)	0.84
Diazinon	1.31 (0.87, 1.96)	0.27
Fonofos	1.63 (1.22, 2.17)	<0.001
Malathion	1.43 (1.08, 1.88)	0.04
Parathion	0.98 (0.53, 1.79)	0.97
Phorate	1.36 (0.96, 1.93)	0.10
Terbufos	1.29 (1.02, 1.64)	0.03

First study to show association with aggressive prostate cancer

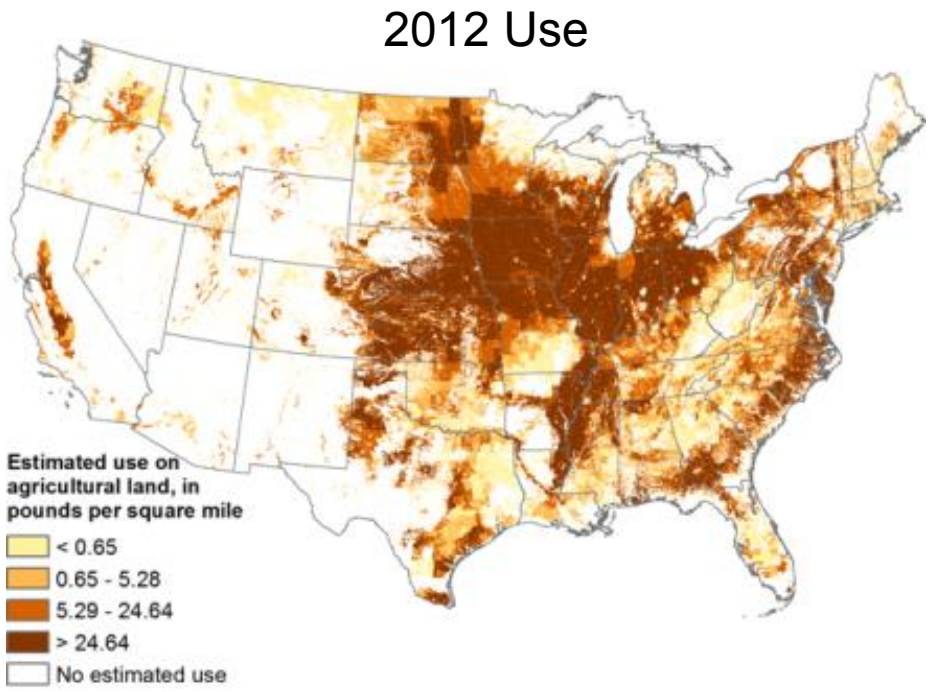
Koutros , Beane Freeman et al., American Journal of Epidemiology, 2014

Association between pesticides and prostate cancer among men with risk allele identified in genome-wide association studies

Gene/Region	Pesticide	Non-exposed	Low exposed OR (95% CI)	High exposed OR (95% CI)	P-int
8q24, rs4242382	FONOFOS	REF	1.2 (0.7, 2.2)	2.9 (1.5, 5.9)	0.002
8q24, rs1447295	FONOFOS	REF	1.1 (0.6, 2.0)	2.8 (1.4, 5.6)	0.003
8q24, Region 3	TERBUFOS	REF	1.5 (0.9, 2.5)	1.8 (1.0, 2.8)	0.02
EHBP1	MALATHION	REF	2.2 (0.9, 5.1)	3.4 (1.4, 8.2)	0.003
PDLIM5	TERBUFOS	REF	1.4 (0.9, 2.1)	1.6 (1.0, 2.5)	0.04
17q24	TERBUFOS	REF	1.7 (1.0, 3.0)	2.1 (1.2, 3.6)	0.03

Koutros, Beane Freeman et al., Cancer Research, 2010
Koutros...Beane Freeman PLoS One, 2013

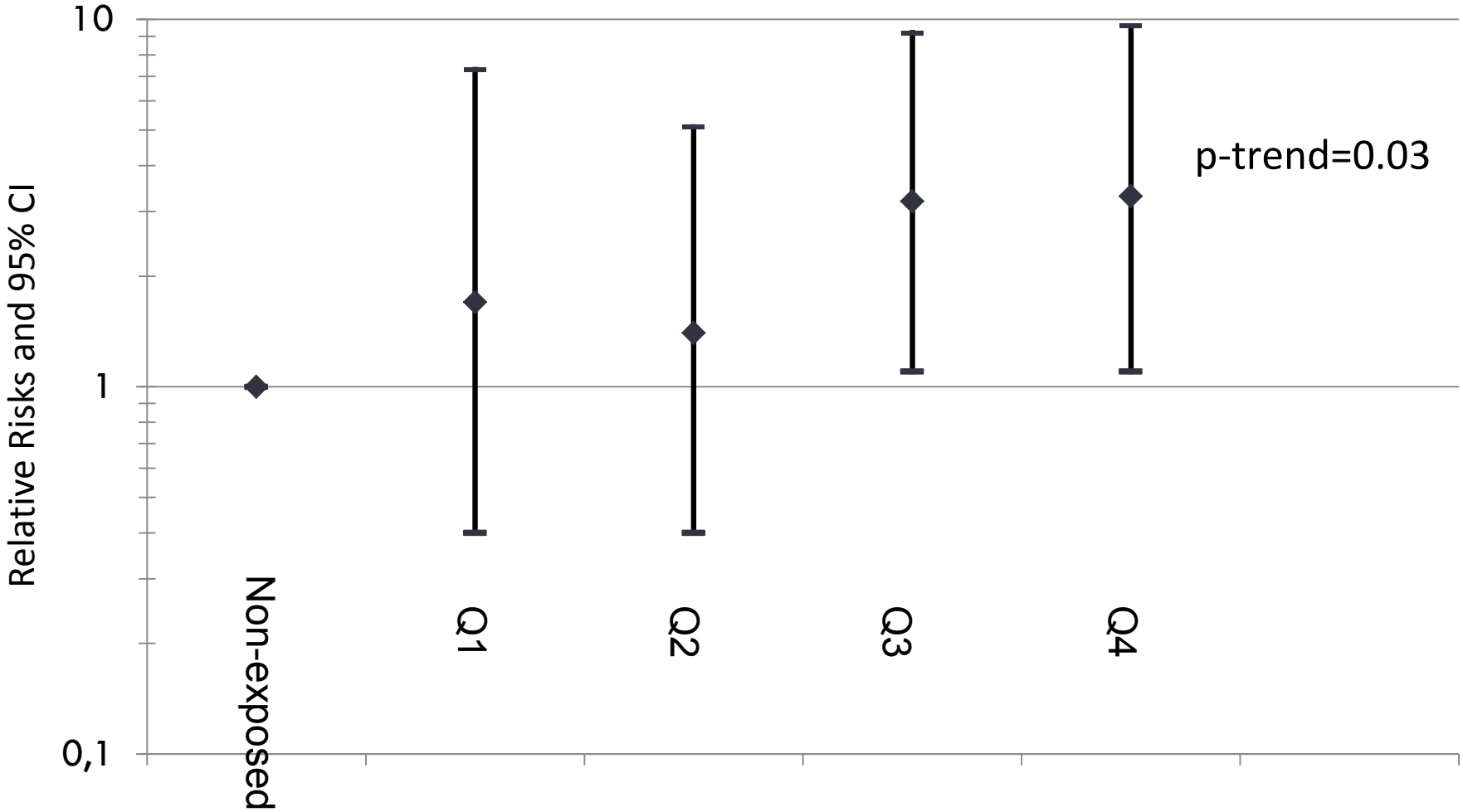
Metolachlor: Chloroacetilinide Herbicide



- Used primarily on corn
- EPA Class C, Possible Human Carcinogen
- Based primarily on liver tumors in rats

Source: USGS Pesticide Use Maps

Metolachlor and Liver Cancer



Silver…Beane Freeman, Int J Cancer, 2015

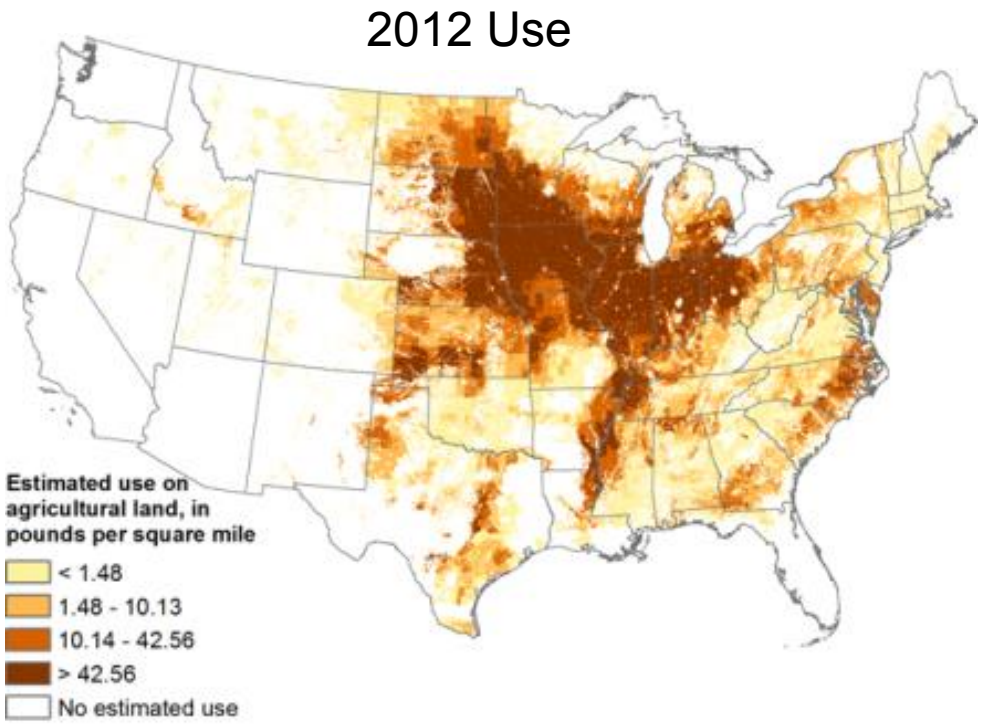
Mixtures Can Be Important

- Important to evaluate individual active ingredients
- Pesticides often applied as mixtures of different products

- May have synergistic effects

Chloroacetilinide Herbicides: Acetochlor

- Registered for use in 1994
- Registration based on reduction in use of other herbicides including atrazine



Source: USGS Pesticide Use Maps

Acetochlor/Atrazine and Lung Cancer

Lung Cancer	
Acetochlor alone	1.96 (0.70-5.50)
Atrazine alone	1.3 (0.9-1.9)

Lerro… Beane Freeman, Int J Cancer, 2015

Acetochlor/atrazine and Lung Cancer

Lung Cancer	
Acetochlor alone	1.96 (0.70-5.50)
Atrazine alone	1.3 (0.9-1.9)
Atrazine + Acetochlor	2.33 (1.30-4.17)

Lerro… Beane Freeman, Int J Cancer, 2015

Cancer in Women

32,345 spouses of farmers enrolled in AHS

60% used pesticides at enrollment

Information on ever/never personal use

Personal Diazinon Use and Cancer Among Spouses

Cancer Site	Exposure	Relative Risk
Breast	Any OP	1.2 (1.0-1.4)
	Diazinon	1.1 (0.3-1.4)
Ovary	Any OP	1.5 (0.8-2.7)
	Diazinon	1.9 (1.0-3.4)

Lerro…Beane Freeman, Occup Environ Med, 2015

Controlled for age, state, smoking, alcohol, BMI, education, menopausal status, parity, OC use, and correlated pesticides

Cancer in Women

32,345 spouses of farmers enrolled in AHS

60% used pesticides at enrollment

All are married to a farmer who applies pesticides

Potential for non-occupational exposures

Non-occupational Pesticide Exposure

- Represent high level of general population exposures
- Important to consider impact of occupational pesticide use on general population in rural areas
  - Proximity to fields/agricultural drift
  - Para-occupational (take-home)
  - Residential use
- Follow up on associations we observed in farmers

Deziel, Friesen…Beane Freeman, Environmental Health Perspectives, 2015
Deziel, Beane Freeman…Friesen, Submitted

Other Agricultural Exposures

Biologically Active Dusts/Endotoxins

Agricultural Exposures and Lung Cancer

- Lung Cancer
- Standardized incidence ratio = 0.48 (0.44, 0.53)
- Due partially to lower smoking rates
- Endotoxins—linked to ↓ lung cancer rates
  - Components of Gram (-) cell walls
  - Found in agricultural settings, including animals and stored grain/hay

Koutros…Beane Freeman, JOEM 2010
Lenters, Basinas, Beane Freeman et al, Cancer Causes Control 2010

Animal Exposures and Lung Cancer

Type of Animals	# Exposed Cases	RR (95% CI)
Beef	130	1.0 (0.8-1.3)
Dairy	17	1.3 (0.8-2.0)
Hogs	70	1.0 (0.8-1.3)
Sheep	5	0.7 (0.3-1.7)
Poultry	22	0.6 (0.4-0.97)
Number of livestock		
None	171	1.0
<100	115	1.1 (0.2-1.5)
100-999	60	0.9 (0.8-1.3)
1,000+	12	0.5 (0.3-0.97)
		p-trend=0.04

Beane Freeman, et al., Cancer Causes Control 2012

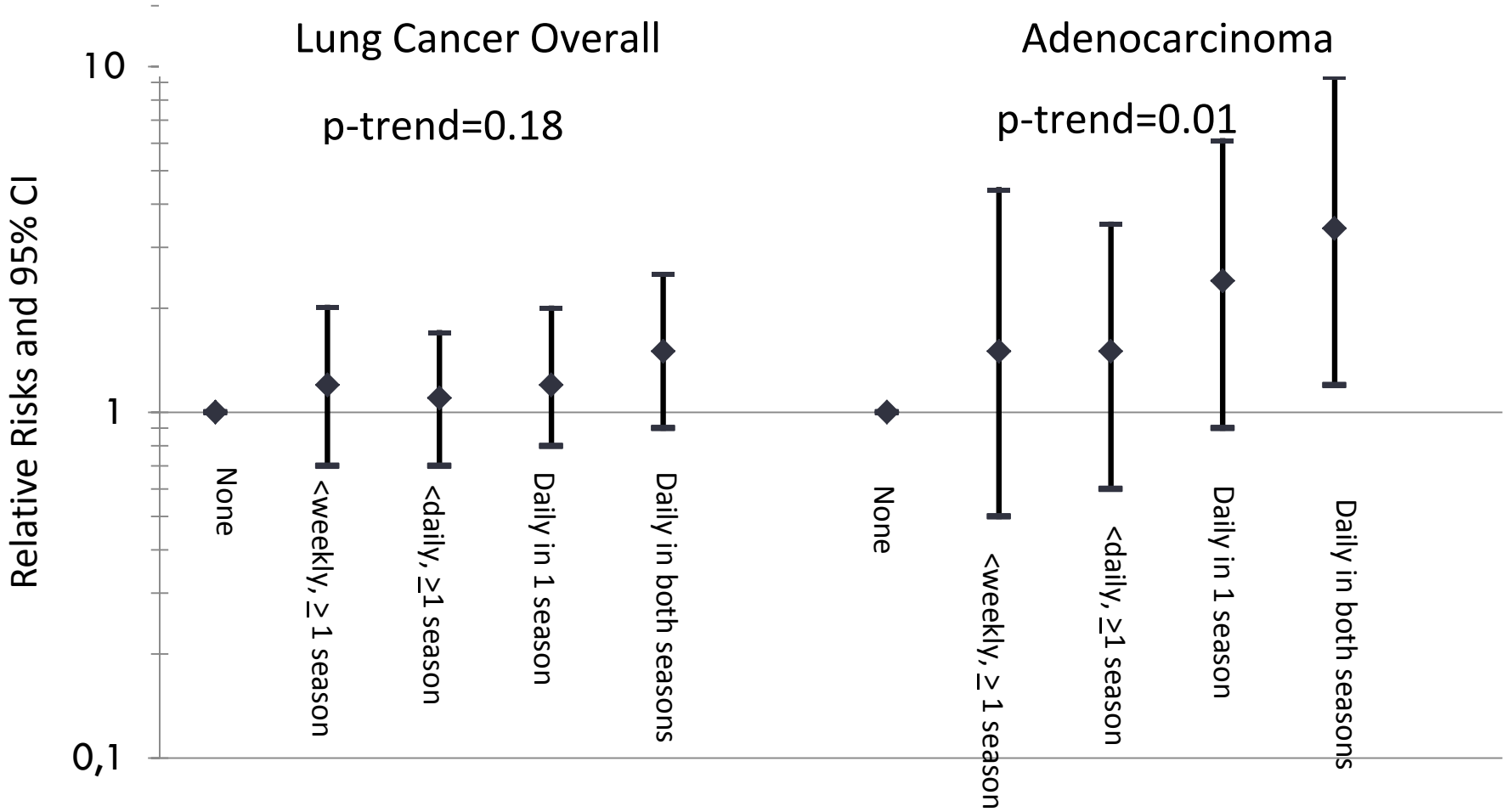
Adjusted for age, state, education and smoking

Lung Carcinogens on the Farm

Diesel exhaust

IARC Group 1 lung carcinogen

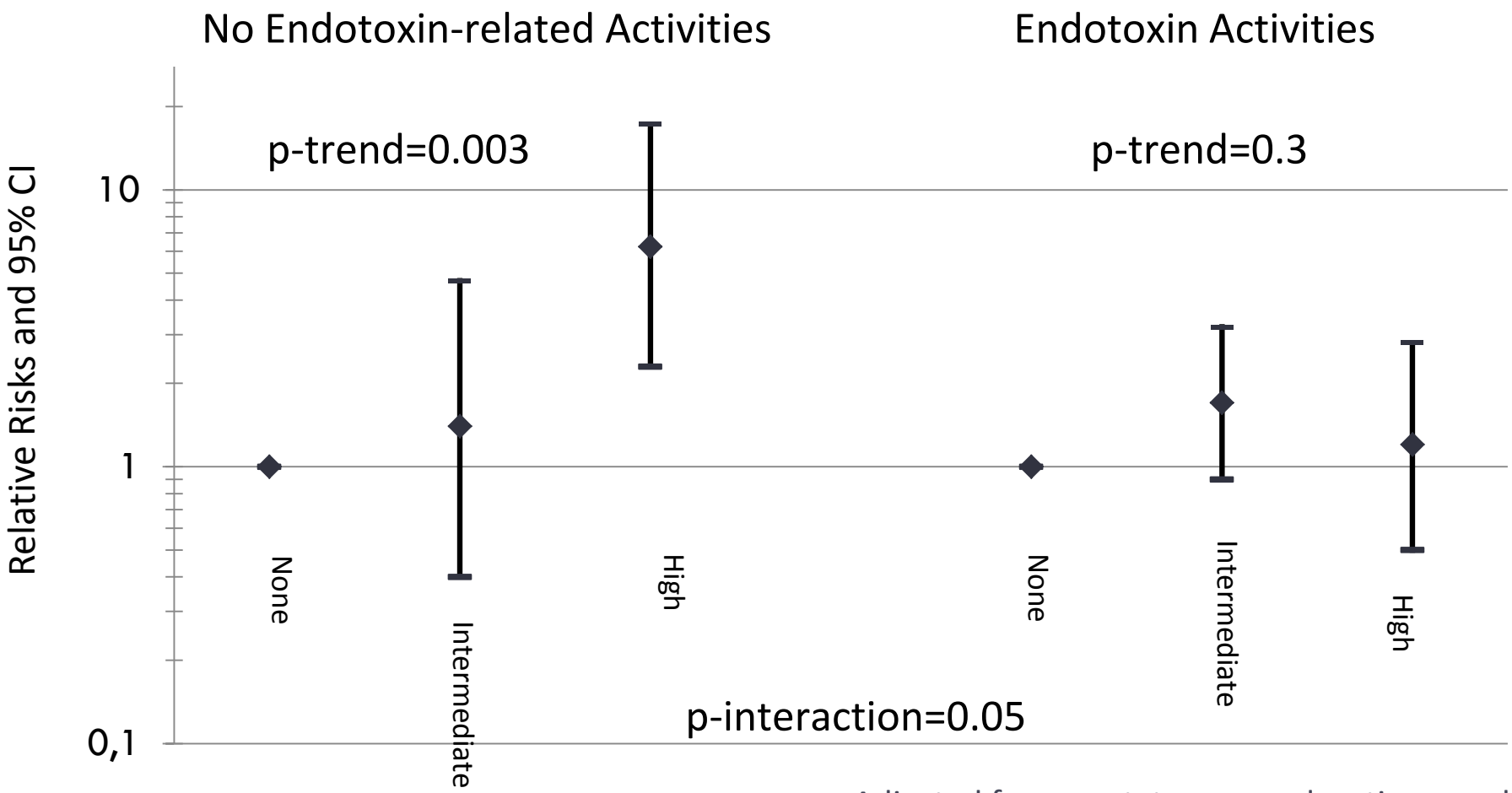
Dieselized Farm Equipment Use and Lung Cancer in Farmers



Adjusted for age, state, race, education, smoking, animal exposure

Tual…Beane Freeman, In Press, Environ Hlth Perspectives

Dieselized Equipment and Adenocarcinoma by Endotoxin Exposure



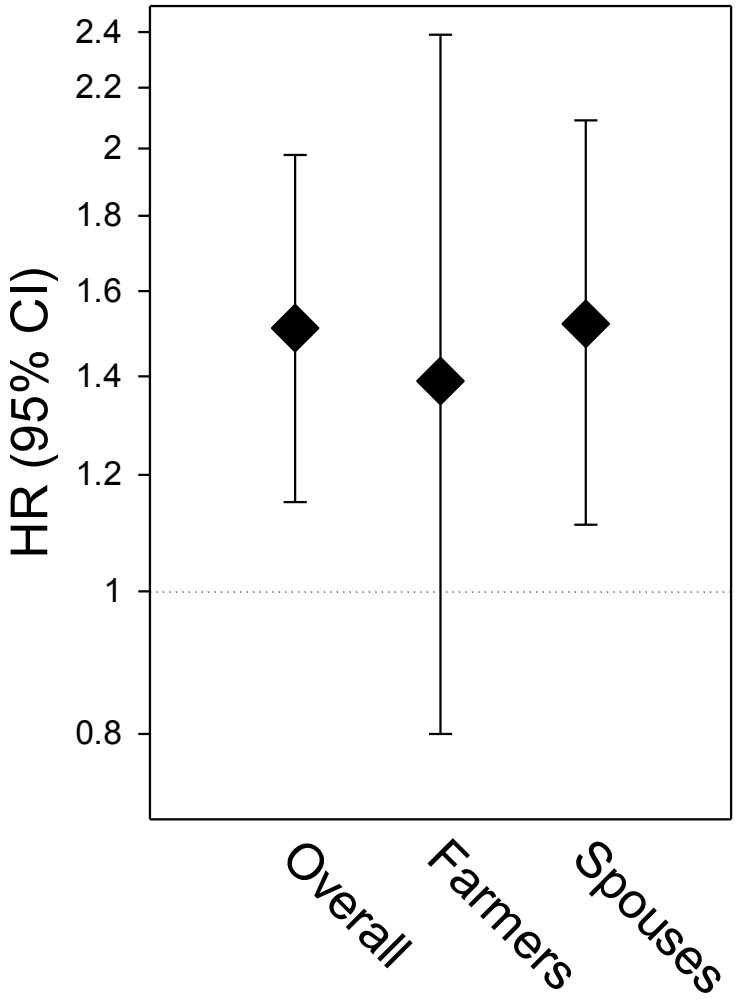
Tual…Beane Freeman, In Press, Environ Hlth Perspectives

Early Life Exposures

Early Life Exposures: Future Cancer Risk?

- 92% of farmers
- 60% of spouses grew up on a farm

Increased risk of NHL among those who grew up on a farm



Hofmann…Beane Freeman, CEBP 2015

Adjusted for sex, state, race, family history, alcohol, smoking, and BMI

Allergies and NHL

- Living on a farm, particularly during childhood
  - ↓ prevalence of allergies
- Potential immune effects
  - Th1/Th2 balance
  - Enhanced T_{reg} activity
  - Increased IL-10 production
- In AHS:
  - Decreased risk of NHL with allergies at enrollment
  - HR=0.6 (0.5-0.8)

Hofmann…Beane Freeman, CEBP 2015

What's next? Mechanistic Insights

Molecular studies evaluating mechanisms of specific pesticide disease associations

- Intermediate effect biomarkers
  - Epigenetics
  - Hormones
  - Inflammation
- Disease precursors
- Somatic mutations in tumor tissue
- Gene-environment interactions

Summary

- Specific pesticides may influence cancer risk for both farmers and those not occupationally exposed:
  - High quality human studies with information on specific chemicals/exposures necessary for public health
- Other exposures on the farm may also be important
- Non-occupational adult and early life exposures

Collaborators

NCI
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North Carolina State University
Jane Hoppin
Environmental Protection Agency
Kent Thomas

The Agricultural Health Study

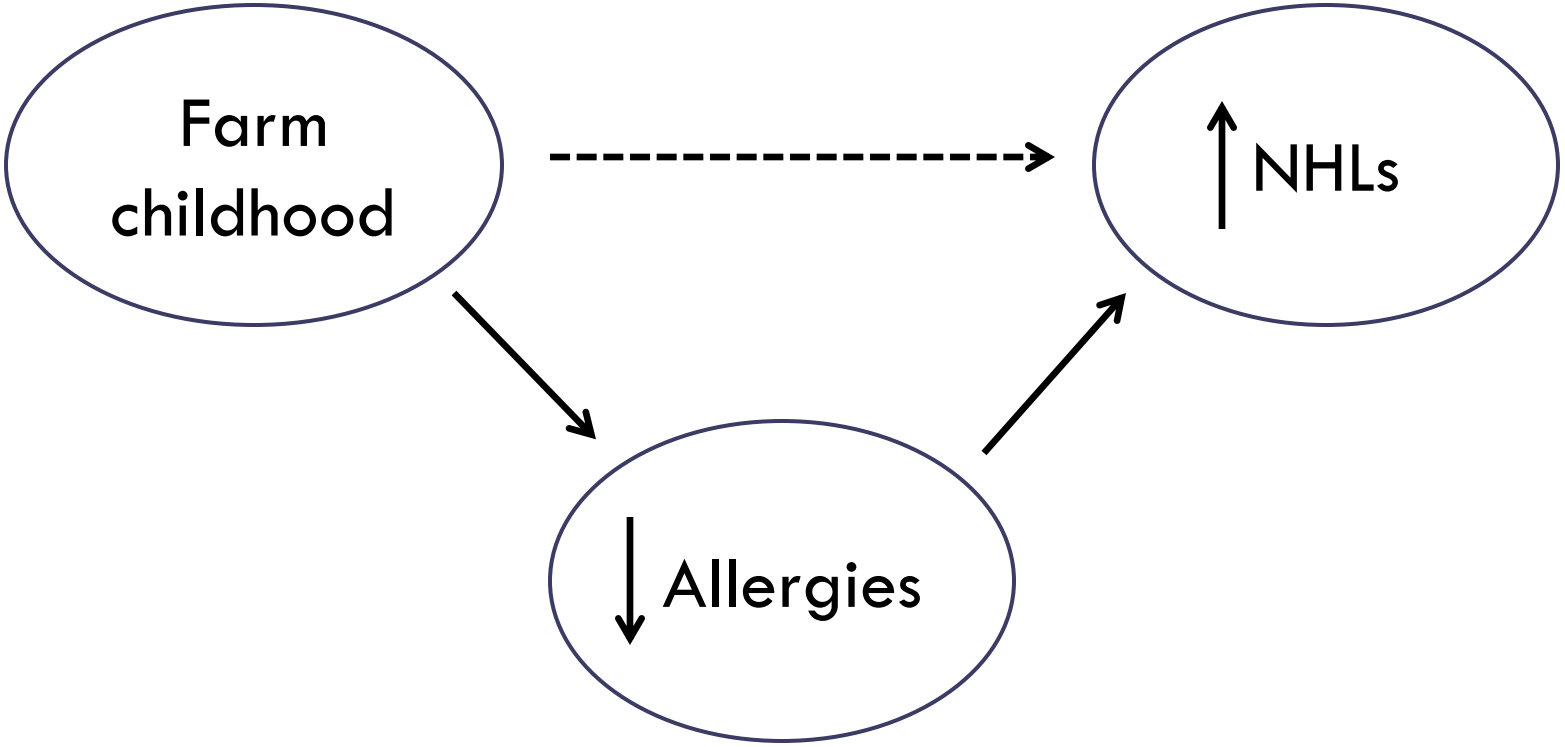
www.aghealth.nih.gov

Early Life Pesticide Exposures: Future Cancer Risk?

- Data on 38,000 children of AHS participants
- Early evaluation showed increased risk of
  - Lymphoma
  - Brain tumors

Now linking to parental exposures

Farm exposures, allergies, and risk of NHLs



Association between pesticides and prostate cancer among men with risk allele GWAS

Increased risk of prostate cancer with several organophosphate insecticides