

Lessons Learned from Agricultural Cohorts

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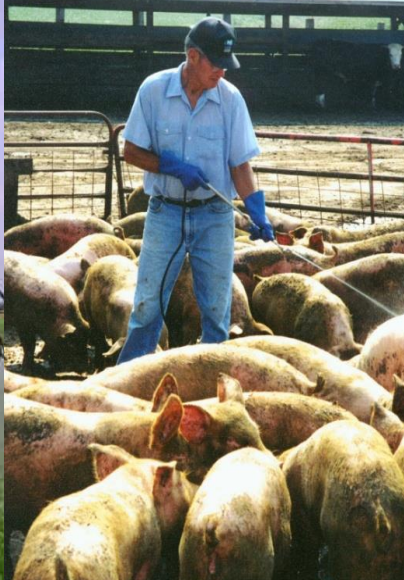
COPLAS

April 4, 2018



What is an Agricultural Cohort?

Industrial Agricultural Practices



Small Farm Agricultural Practices



Background: Agriculture and Health

- Some historical general characteristics of agricultural populations
 - Low rates of tobacco and alcohol use
 - High rates of physical activity
- Numerous exposures
 - Pesticides
 - Animals
 - Diesel engine exhaust
 - Biologically active dusts
 - Zoonotic microbes
 - Fuels, oils, and solvents

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What Are Pesticides?

Diverse group of chemicals designed to kill living organisms

Herbicides



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Herbicides

Insecticides



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Herbicides

Insecticides

Fungicides



What Are Pesticides?

Diverse group of chemicals designed to kill living organisms

Herbicides

Insecticides

Fungicides

Rodenticides



Pesticides

- 2.4 billion kg pesticide active ingredients applied worldwide in 2007
- >1 billion people occupationally exposed worldwide
- >800 different active ingredients currently registered for use in the U.S.
- Very few have been evaluated formally for human carcinogenicity or other post-market health effects

Pesticides: Not just an agricultural exposure

- 90% of U.S. population has detectable levels of pesticides or metabolites in their urine (Source: NHANES)
- Exposure sources:
 - Residential use



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- Exposure sources:
 - Residential use
 - Drift from agricultural use
 - Food and water contamination



**What's
on my
food?**

How Can We Study Effects of Pesticides?

- Need information on specific active ingredients
Toxicity differs among chemicals even in the same class
- Highly exposed population for evaluation small effects
- Accurate characterization of exposure for exposure-response
- Agricultural populations good choice and can inform general population health

Agricultural Health Study

- Two agricultural states:



Agricultural Health Study

NCI/NIEHS/EPA/NIOSH

- 57,000 licensed pesticide applicators (farmers)
- 32,000 spouses (may apply pesticides themselves or have bystander exposure)
- 17+ years of follow-up
- >12,000 incident cancers

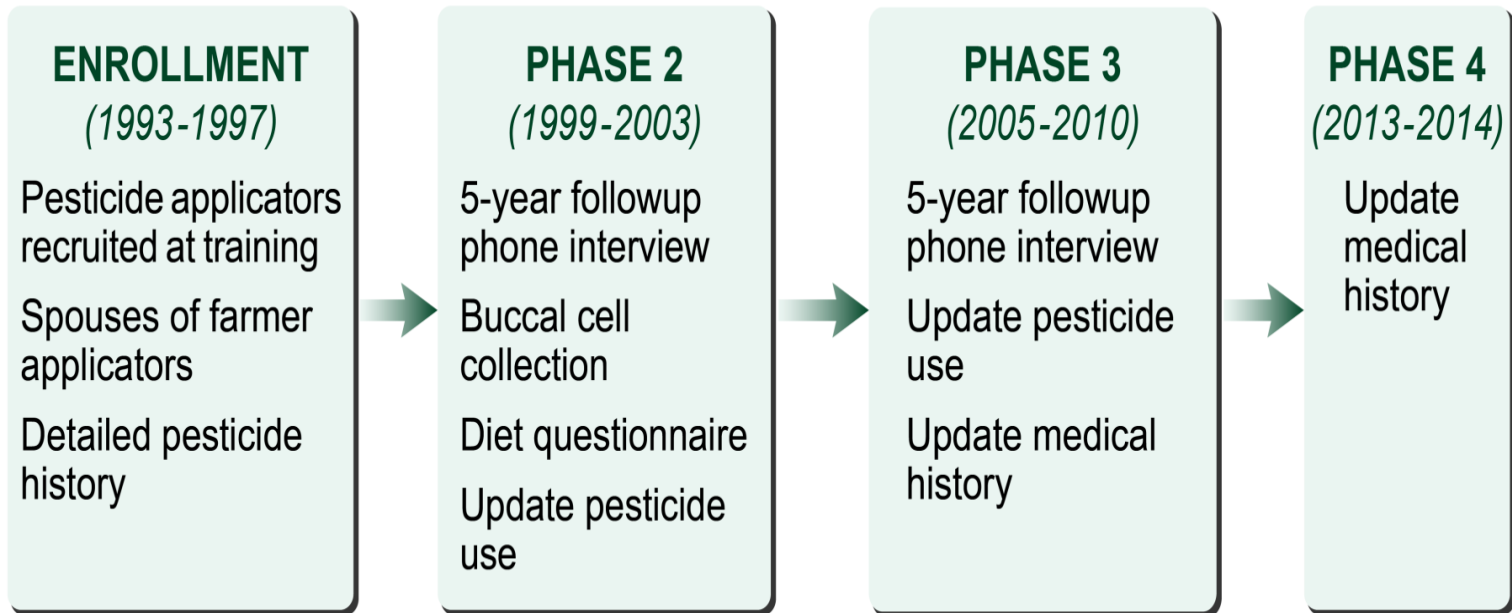




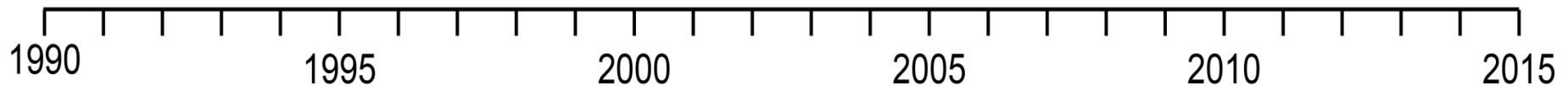
The Agricultural Health Study

- Designed to study a wide range of health effects of agricultural exposures in farmers and their families
- Includes specific information on use of individual pesticide active ingredients
 - Lifetime
 - Current
 - Use of personal protective equipment
 - Method of application
 - Other information that may modify exposure intensity

AHS Timeline



Cancer and Mortality Followup



Standardized Cancer Incidence Ratios in the AHS



Cancer site	Private applicators		Spouses	
	N=52,394		N=32,346	
	N	SIR	N	SIR
All	4,316	0.85	1,896	0.82
Lung & Bronchus	436	0.48	133	0.42
Ovary	9	2.45	58	0.72
Prostate	1,719	1.19	7	1.05
Multiple myeloma	71	1.20	21	0.94
NHL	195	0.99	86	0.99
Leukemia	133	0.96	37	0.83
Breast	33	0.95	770	1.0
Colon	339	0.9	144	0.83

Selected Cancer Findings and Mechanistic Clues

Organophosphate Insecticides

Organochlorine Insecticides

Chloroacetinilide Herbicides

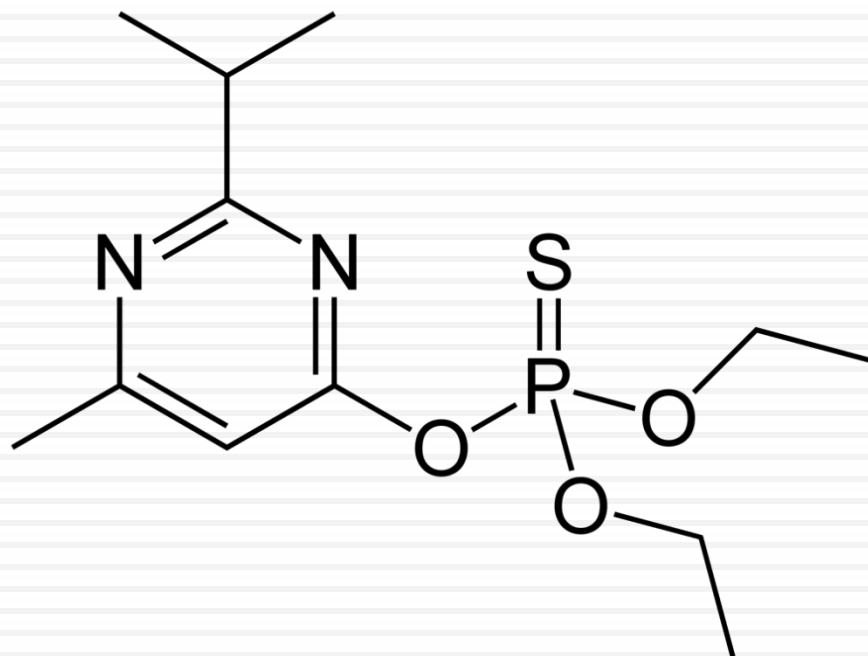
Pyrethroids

Organophosphate Insecticides

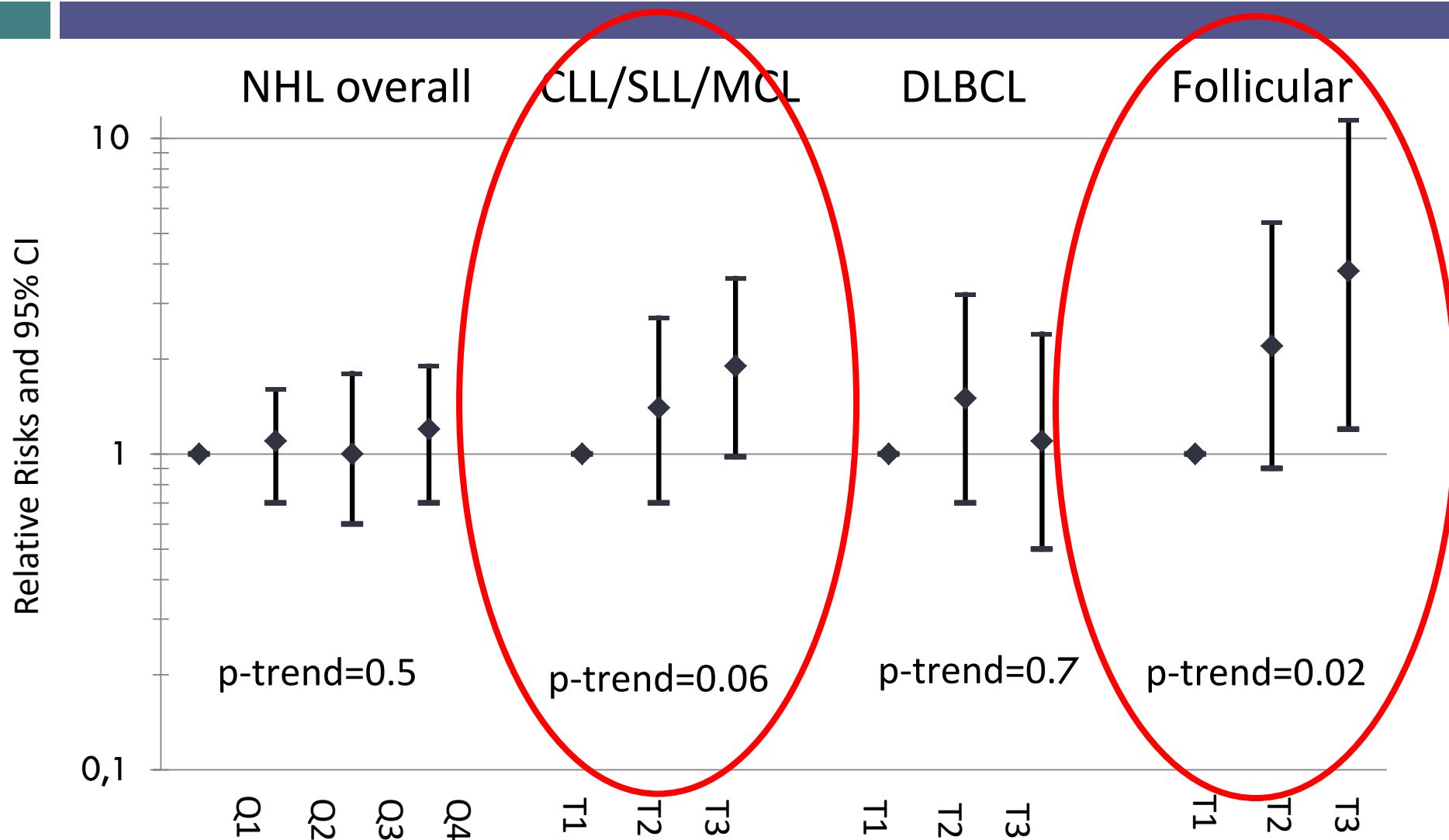
- Introduced in the 1960s
- Widespread use on crops and animals, agricultural and residential use (historically)
- Acetylcholinesterase inhibition



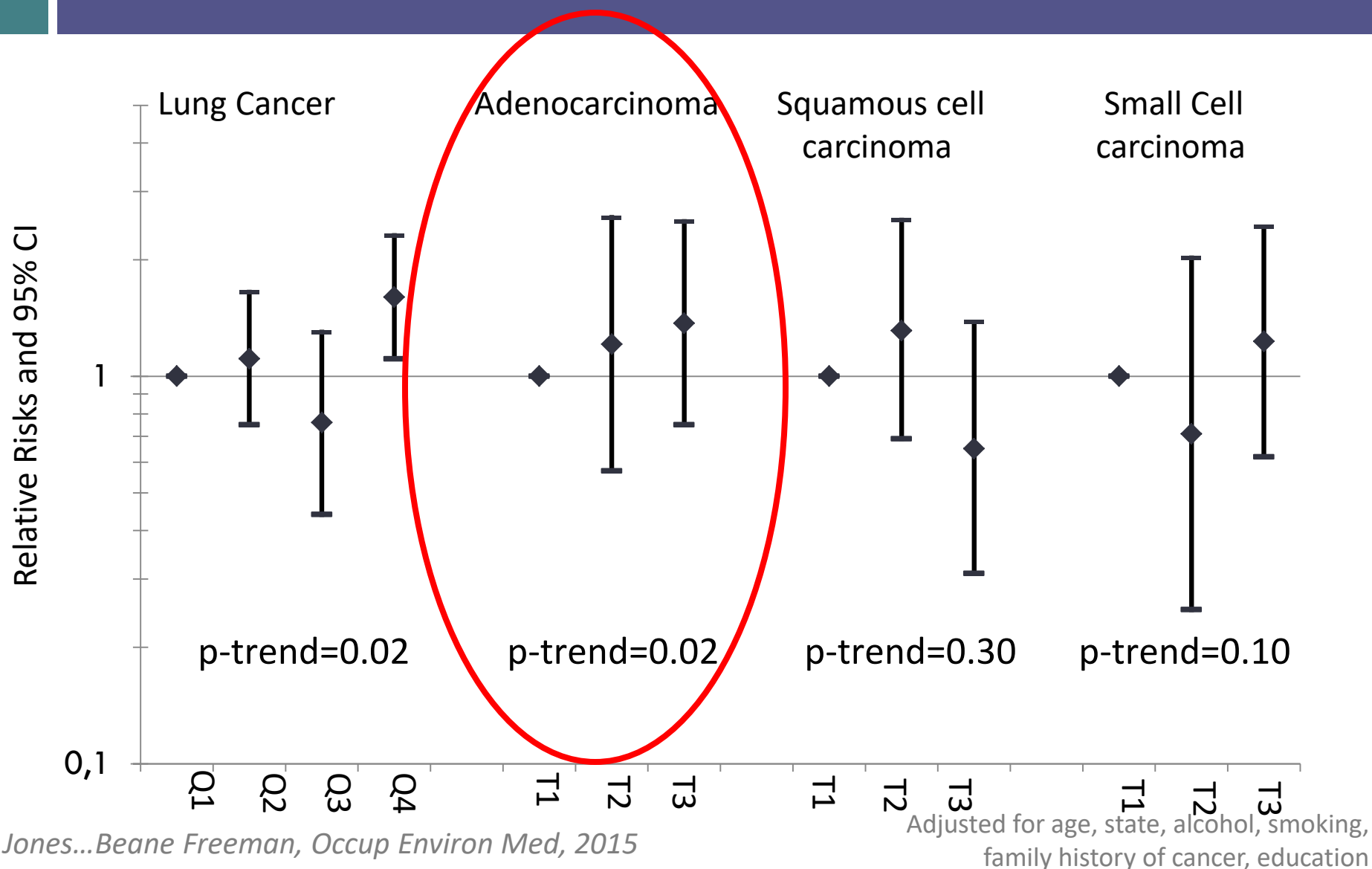
Diazinon



Diazinon and NHL



Diazinon and Lung Cancer



Diazinon Use and Cancer Among Women

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)

Organophosphate Insecticides and Aggressive Prostate Cancer

<u>Organophosphate Insecticide</u>	<u>Q4 vs. Non-exposed</u> <u>RR 95 % CI</u>	<u>P-trend</u>
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 GWAS

Several loci for prostate cancer identified through genome-wide association studies (GWAS)

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
<i>EHBP1</i>	MALATHION	REF	2.2 (0.9, 5.1)	3.4 (1.4, 8.2)	0.003
<i>PDLIM5</i>	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

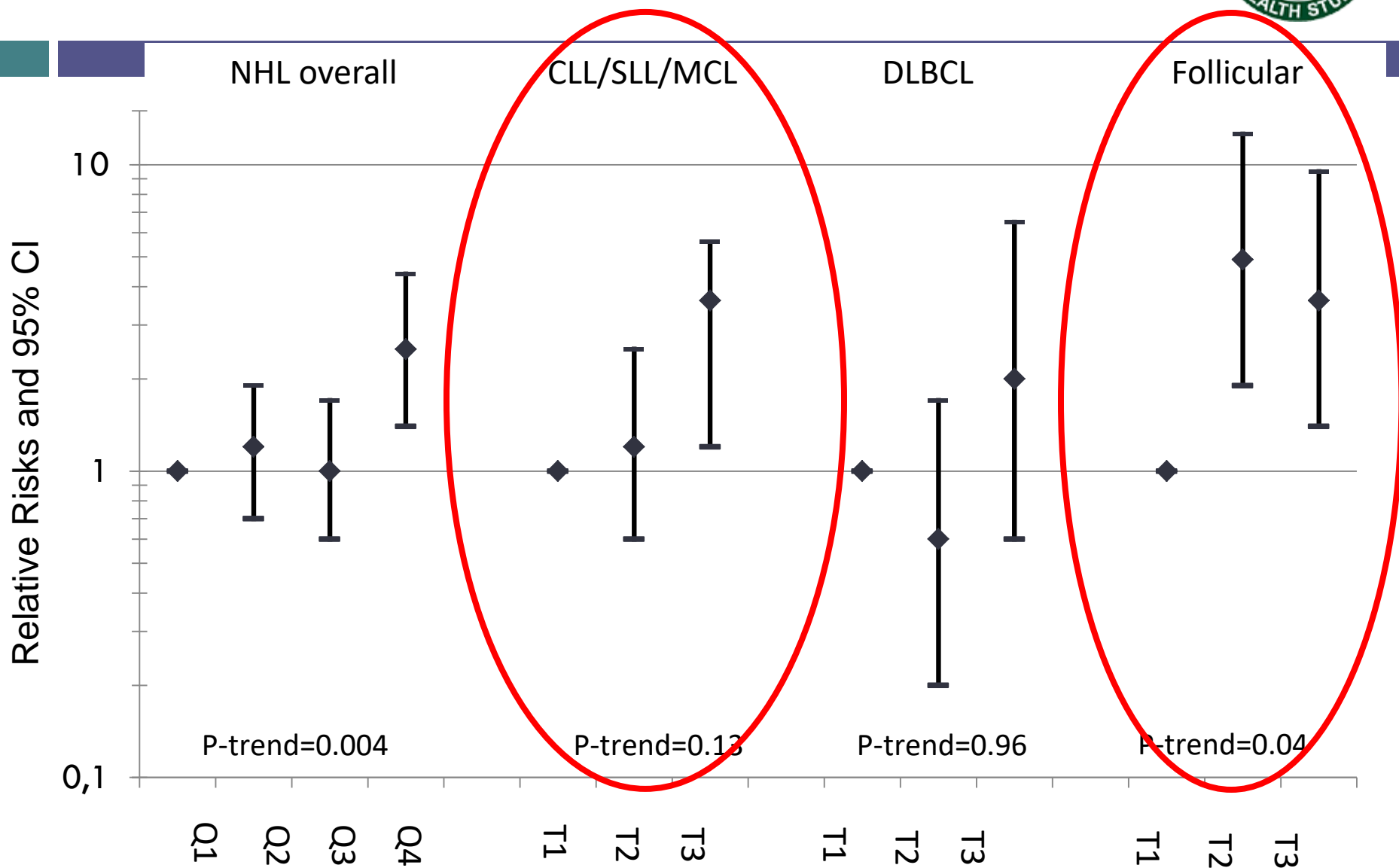
Koutros...Beane Freeman PLoS One, 2013

Organochlorine Insecticides

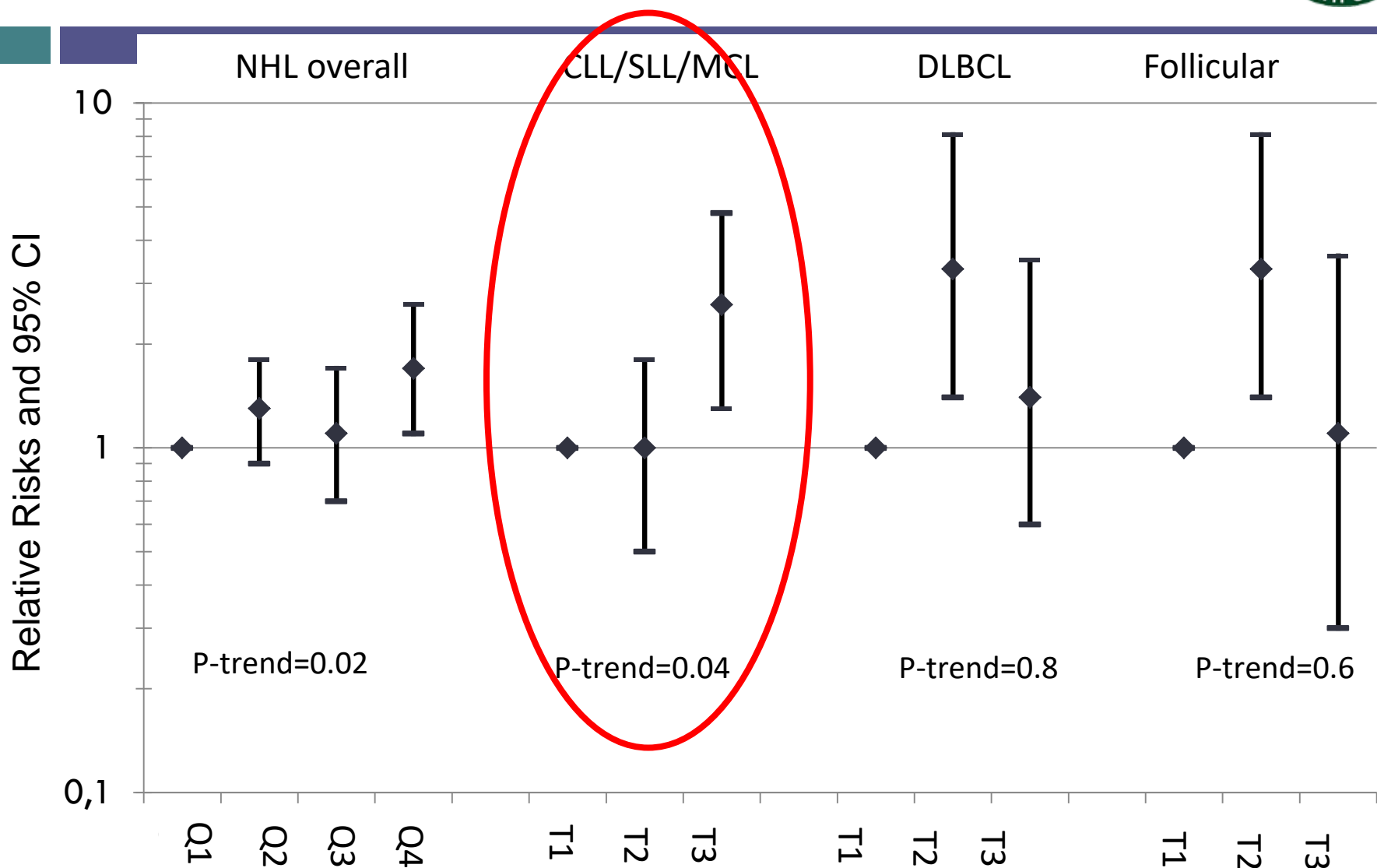
- Introduced in the 1940s
- Persistent
- Most banned in US in 1970s
 - Lindane still used until 2006
- Many still used in developing world for vector control



Lindane and NHL



DDT and NHL



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
[https://doi.org/10.1016/S1473-0245\(15\)00081-9](https://doi.org/10.1016/S1473-0245(15)00081-9)

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

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



Published Online
March 20, 2015
[https://doi.org/10.1016/S1473-0245\(15\)00081-9](https://doi.org/10.1016/S1473-0245(15)00081-9)

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

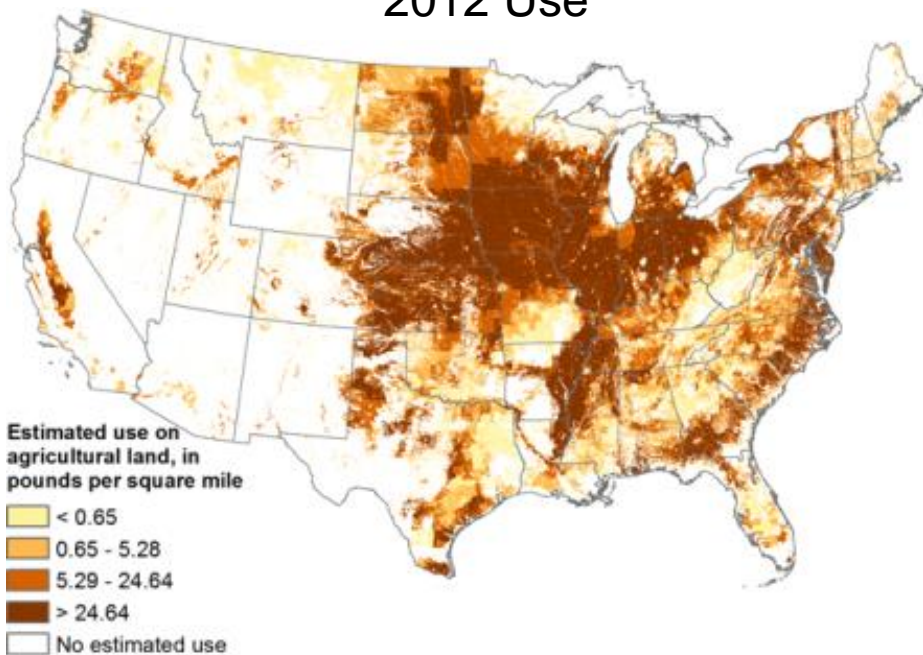
The insecticides malathion and diazinon were classified as "probably carcinogenic to humans" (Group 2A). Malathion is used in agriculture, public health, and residential insect control. It continues to be produced in substantial volumes throughout the world. There is limited evidence in humans for the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

[*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)

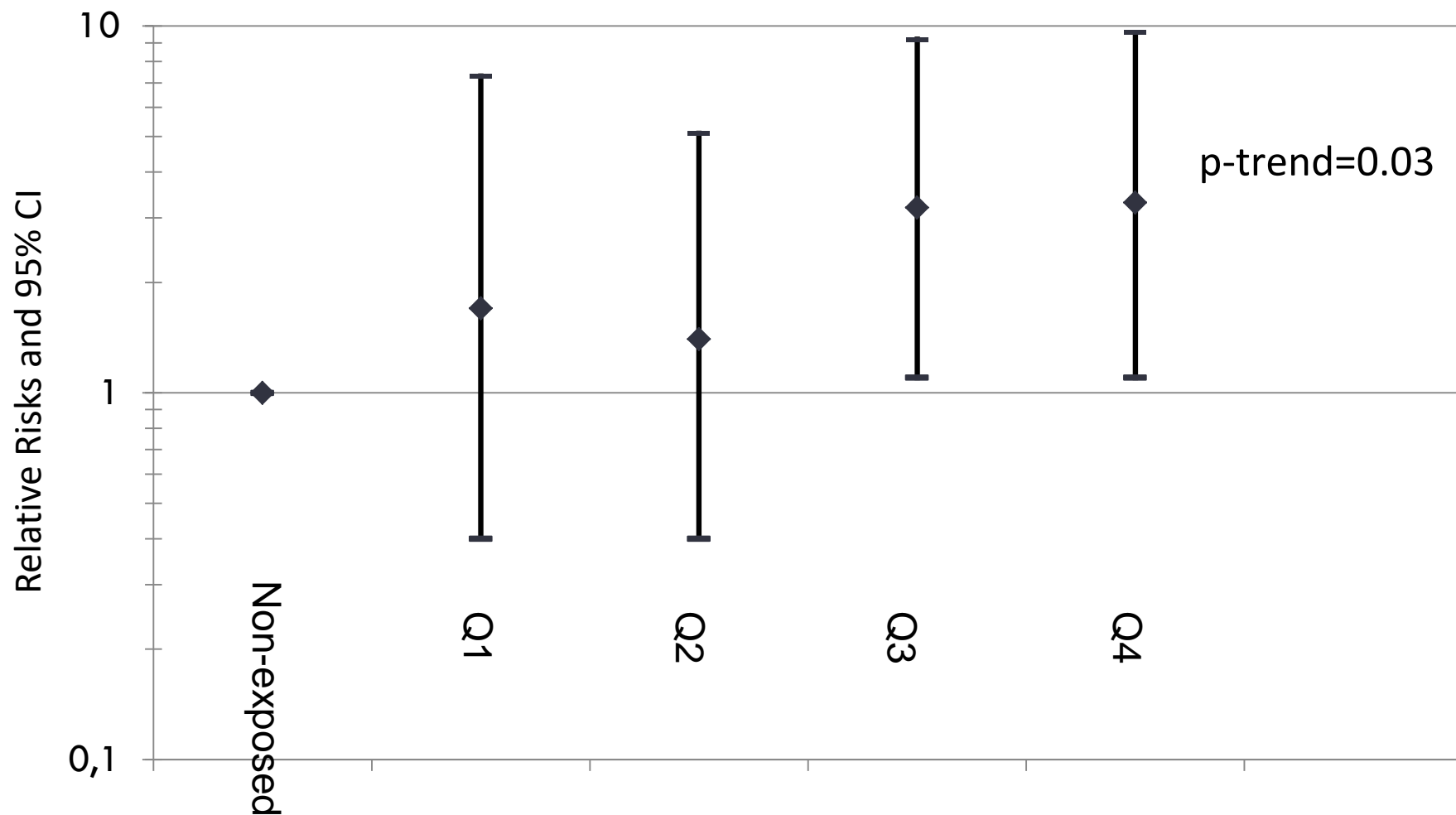
Metolachlor: Chloroacetilide Herbicide

2012 Use



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

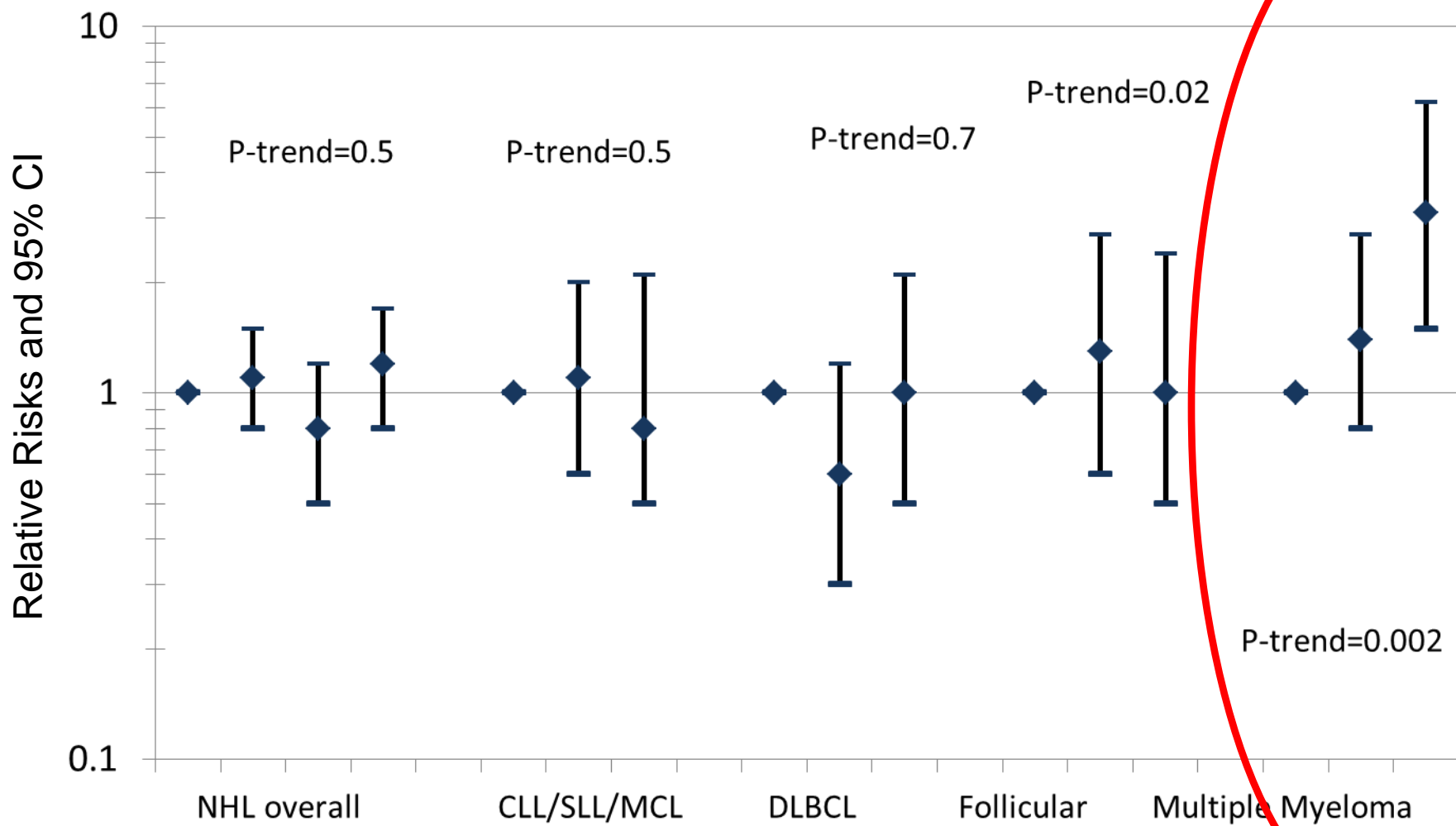
Metolachlor and Liver Cancer



Multiple Myeloma

- A largely incurable neoplasm of plasma cells characterized by an overproduction of monoclonal immunoglobulins
- Etiology not well understood, occurs in excess among farmers in multiple studies
- Highly fatal
- Monoclonal Gammopathy of Undetermined Significance (MGUS) → Multiple Myeloma

Results: Permethrin



Risk of MGUS in AHS vs. Olmstead County, MN

Population	Total, n	MGUS, n	OR (95% CI)
Olmstead County	9,469	350	1.0 (ref)
AHS cohort	555	38	1.9 (1.3-2.7)

-Landgren O et al., Blood (2009); 113(25):6386-6391

Ongoing work: Examine risk of MGUS in larger population within AHS to link to permethrin exposure (J. Hofmann, PI)

Pesticides and Non-cancer Outcomes

Allergic asthma

Parkinson's Disease

Background: Allergic Asthma

Growing up on a farm is associated with decreased risk of allergies (Hofmann 2016)

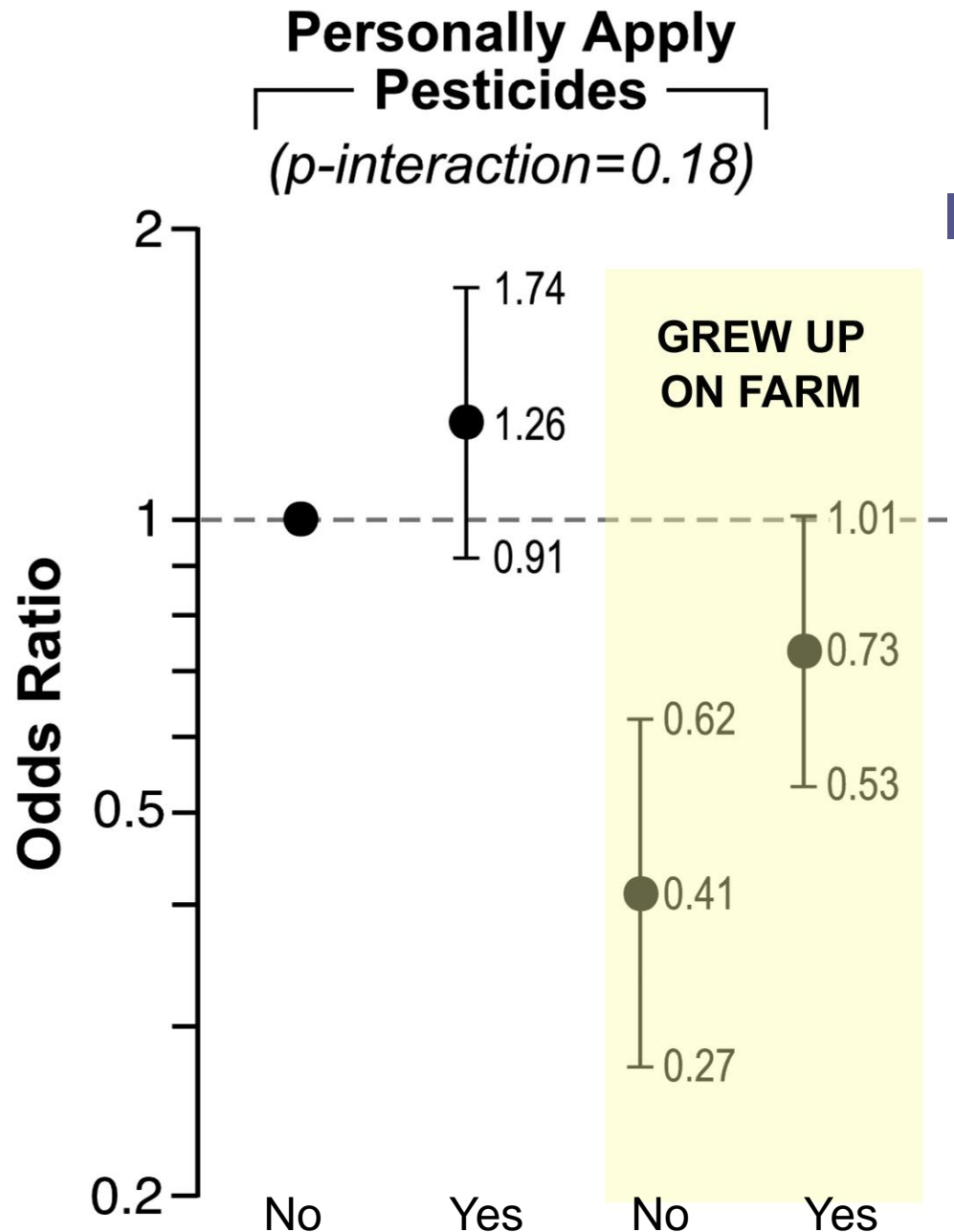
Human data suggest:

Organophosphates are associated with wheeze among farmers (Hoppin 2002, 2006, Ohayo-Mitoko 2000; Hernandez 2008; Fieten 2009)

Do pesticides modify allergic asthma risk?

Odds ratios of allergic asthma among farm women, stratified by growing up on farm.

Applying pesticides can reduce the protective effect of growing up on the farm.



Organophosphates and Allergic Asthma

	Chlorpyrifos	Coumaphos	Parathion
Population	OR (95% CI)	OR (95% CI)	OR (95% CI)
Spouses	1.4 (0.8,2.4)	2.2 (1.0,4.7)	2.9 (1.3,6.2)
Applicators	1.3 (0.9,1.8)	2.3 (1.5,3.7)	2.0 (1.2, 3.5)

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Applicators	1.3 (0.9,1.8)	2.3 (1.5,3.7)	2.0 (1.2, 3.5)
Never use	1.0	1.0	1.0
Low use	1.0 (0.6,1.6)	1.2 (0.5,2.7)	2.2 (1.1,4.3)
High Use	1.4 (0.9,2.2)	3.8 (2.3,6.4)	2.1 (1.0,4.4)
P-value for trend	0.16	0.001	0.01

Background: Parkinson's Disease

- Mitochondrial dysfunction and oxidative stress are suspected underlying mechanisms
- In experimental studies, paraquat and rotenone exhibit these actions
- Study of 110 PD patients and 358 controls within AHS
 - Need clinical confirmation of self-reported disease
 - PD diagnosed by movement disorder specialist

Association of PD and pesticides

Pesticide	OR (95% CI)
Paraquat	2.5 (1.4–4.7)
Rotenone	2.5 (1.3-4.7)

Adjusted for reference age tertile, sex, state, and cigarette smoking.

Evidence that GSTT1 confers protection against oxidative stress

Significant interaction between GSTT1 and paraquat:

OR = 11.1 (95% CI: 3.0-44.6) for paraquat use and GSTT1*0

P interaction: 0.027

Selected Other Findings from the AHS

- Specific pesticides associated with increased risk of:
 - Hypothyroidism
 - Sleep apnea
 - Rheumatoid arthritis
 - Macular degeneration
 - Non-malignant respiratory disease
 - Type I diabetes
 - Hormonal disruption
- Pesticide poisoning and depression
- Many specific cancer-pesticide associations

The Agricultural Health Study



 **Agricultural Health Study**

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The Agricultural Health Study works to understand how agricultural, lifestyle, and genetic factors affect the health of farming populations.

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News & Findings

[2014 Study Update](#)
AHS finds links between use of certain insecticides and aggressive prostate cancer; Pesticide poisoning but not overall pesticide use linked to depression in farmer's wives.

[Publications](#)
AHS-related research has been published in many peer-reviewed journals.

For Collaborators

The Agricultural Health Study is funded by the National Cancer Institute and the National Institute of Environmental Health Sciences in collaboration with the US EPA and NIOSH. The AHS encourages researchers to collaborate with us to focus on specific health issues related to farming practices. These studies are designed to leverage the data collected from participants.

[Collaboration Resources](#)

For Participants

More than 89,000 farmers and their spouses in Iowa and North Carolina have been involved in the AHS since 1993. Their involvement has provided, and continues to provide, the data that researchers need to help the current and future generations of farmers, and their families, live healthier lives.

[Participant Information](#)

www.aghealth.nih.gov

What is needed?

More studies needed to:

- Replicate findings in other populations
- Investigate new chemicals
- Evaluate impact of timing of exposures

Early life?



- More information on risks to general population

What is needed?

Molecular studies evaluating mechanisms of specific pesticide-disease associations

- Intermediate effect biomarkers
 - Epigenetics
 - Hormones
 - Inflammation
 - Genetic alterations

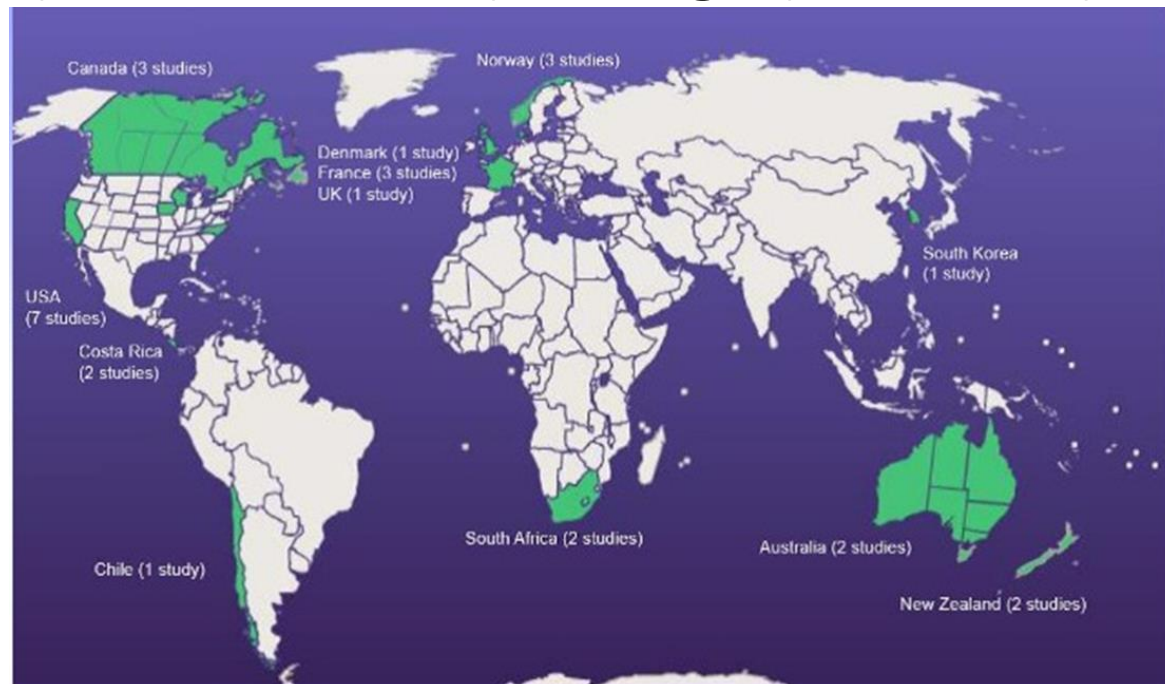
AGRICOH

- Agricultural Cohort Consortium
- Initiated to foster replication and collaboration through data sharing and pooling among agricultural cohorts



AGRICOH

- 30 cohorts included from around the world
- Focused on many outcomes and ag exposures
 - Not just pesticides
- Small (a few hundred) to large (>100,000)



AGRICOH

- Steering Group:
 - Cancer (Laura Beane Freeman, NCI)
 - Respiratory Disease (Jane Hoppin, NC State)
 - Neurologic (Isabelle Baldi, University of Bordeaux)
 - Reproductive outcomes (Paul Romitti, University of Iowa)
 - Exposure Assessment (Hans Kromhout, Utrecht University)
 - Ad hoc (Pierre Lebailly, University of Caen), Jeroen Douwes, Massey University
 - Secretariat (Joachim Schuz, IARC)

AGRICOH: Publications

AGRICOH description: *Leon et al., 2011*

Description of cohorts participating as of 2009 meeting

Membership has grown since then

Pesticide exposure assessment harmonization:

Brouwer et al., 2016

Compares exposure assessment methods across 3 large cohorts and evaluates potential limitations of each

AGRICOH: Current Descriptive Projects

- Cancer incidence and mortality worldwide
- Non-malignant respiratory disease prevalence
- Neurologic disease mortality

Will allow evaluation of similarities and differences across farming practices and exposures

AGRICOH: Current Etiologic Projects

- Pesticides and
 - Hematologic malignancies
 - Prostate cancer
 - Breast cancer (female farm workers and spouses)
- Agricultural animal exposures and hematologic malignancies

AGRICOH

- Membership is open to studies with specific exposure information
 - www.agricoh.iarc.fr
- Periodic meetings of whole group or sub-groups



Conclusions



- Pesticides are important
 - Economically and for vector control
- Represent a diverse group of chemicals (>800) with many mechanisms of action that may not be related to disease
- High quality human studies with information on specific chemicals necessary for public health
- Critical to understand health risks in human populations with these ubiquitous exposures

The Agricultural Health Study



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