Occupational epidemiology in practice: understanding pesticide-cancer risk in the AHS cohort and learned lessons

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10. Health Disparities
11. Air Pollution
12. Pesticide & Cancer
13. Climate & Cancer

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NIH National Cancer Institute

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Pesticide exposures

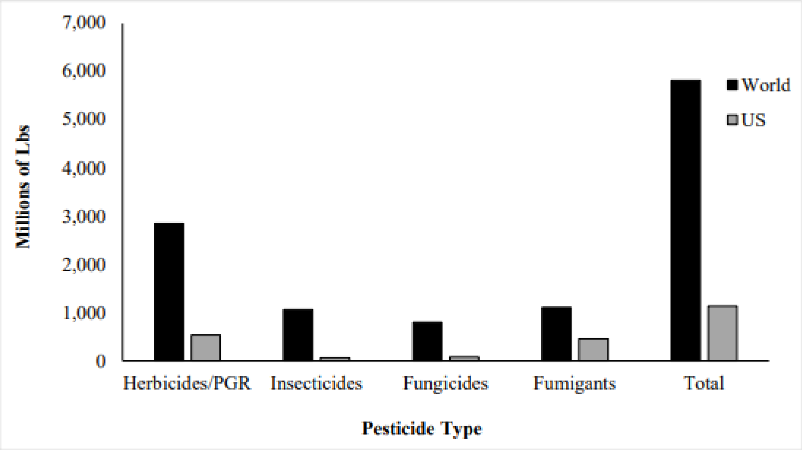
Pesticide exposure everywhere

- 6 billion lbs. of pesticides were applied worldwide in 2011 & 2012
- 11% growth in pesticide use per year 1950-2000
- >90% of US Population has detectable levels of pesticide or metabolites in urine or blood
- Worldwide over 1 billion people are occupationally exposed to pesticides

Carvahlo. Food & Energy Secur. 2017, CDC, 2019, Beane Freeman, EHP. 2022

Pesticides

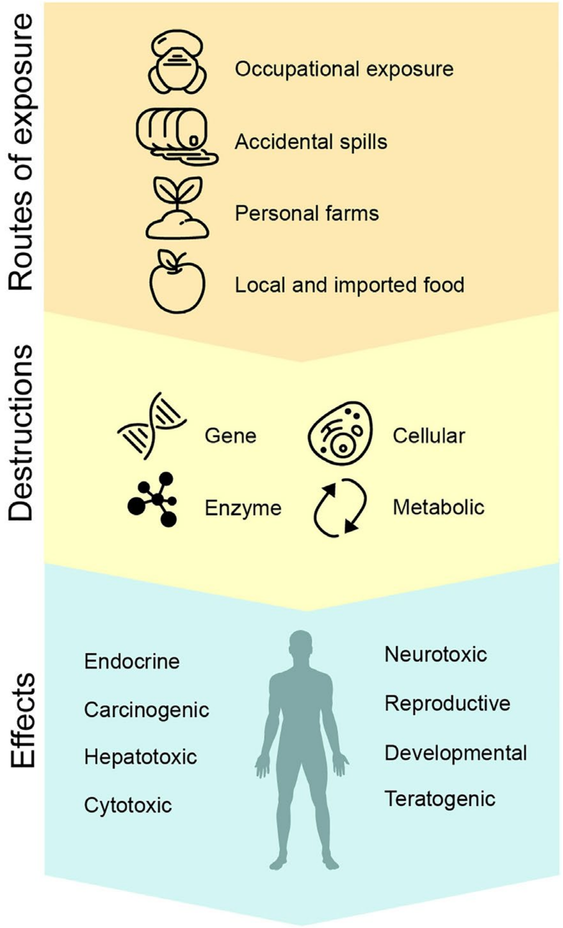
- Encompass many diverse chemical and chemical families
  - Herbicides
  - Insecticides
  - Fungicides
  - Fumigants
  - Rodenticides



Atwood & Paisley-Jones. USEPA. 2017

Human health effects

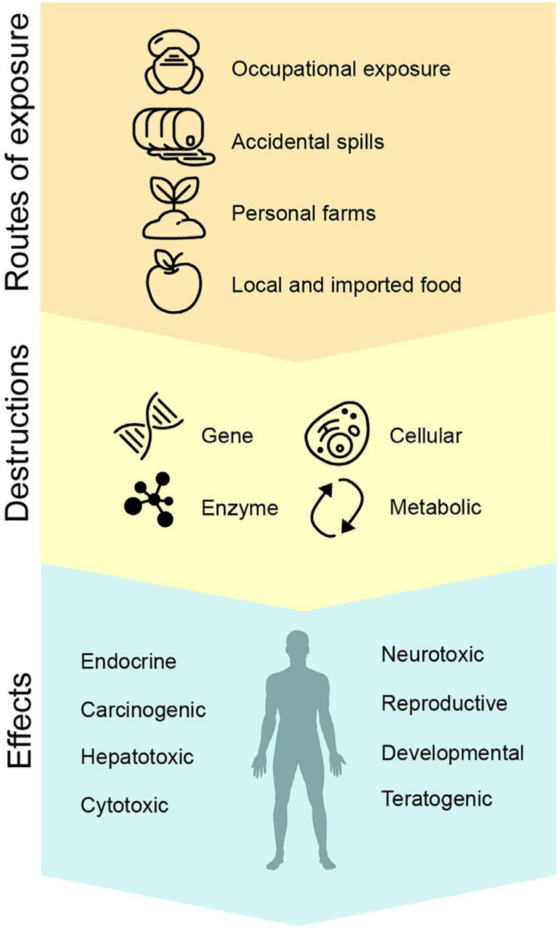
- Health effects of pesticides depend on the type of pesticide
- Active ingredients from pesticides subject to toxicity testing and registration
  - Experimental, in vitro study designs
- Not much post-market health effect studies available in the US



Kalyabina et al. Tox Reports. 2021

Human health effects

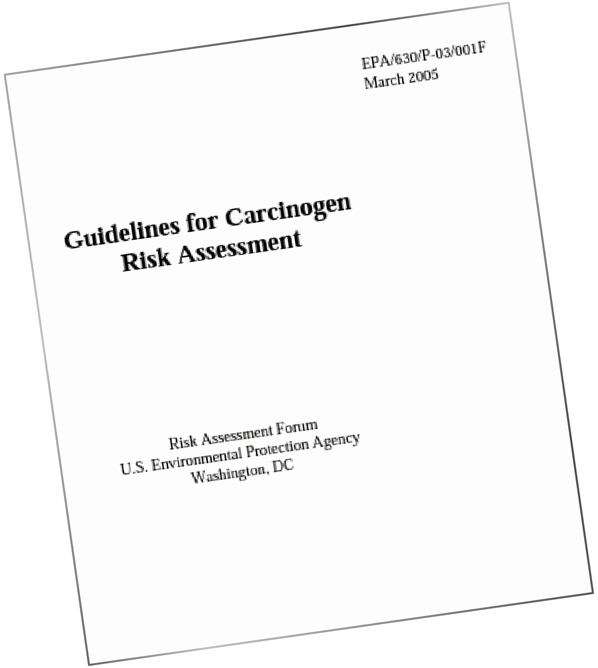
- Limited studies among humans
- Systematic reporting for accidental poisoning/acute exposures
  - National Poison Data System, OPP Incident Data System, National Pesticide Info Center, CDC/NIOSH SENSOR-Pesticides, CA Pesticide Illness Surv Program
- Human population studies
  - Different study designs for many different questions
  - Particularly for chronic diseases



Kalyabina et al. Tox Reports. 2021

Risk Assessment of Pesticides by USEPA

- USEPA, Office of Pesticide Programs
  - Pesticide regulation enshrined by the Federal Insecticide, Fungicide, Rodenticide Act (FIFRA)
  - Review pesticides registration on a rolling basis
- Classification of Carcinogens, Weight of Evidence Approach (2005)
  - Carcinogenic to humans
  - Likely to be carcinogenic to humans
  - Suggestive evidence of carcinogenic potential
  - Inadequate information to assess carcinogenic potential
  - Not likely to be carcinogenic to humans pesticide



EPA/630/P-03/001F
March 2005

Guidelines for Carcinogen Risk Assessment

Risk Assessment Forum
U.S. Environmental Protection Agency
Washington, DC

Occupational vs. Environmental Pesticide Exposures

Occupational

- Manufacturing
- Mixing, loading, applying pesticides
- Working in treated fields/ re-entry tasks
- **Intermittent**, “**higher**” **exposures**

Environmental

- Diet, drinking water, agricultural drift
- Home, lawn, and pet applications
- “**Lower**” **exposures**

Pesticide exposure assessment

Characterizing Exposure to Individual Pesticides

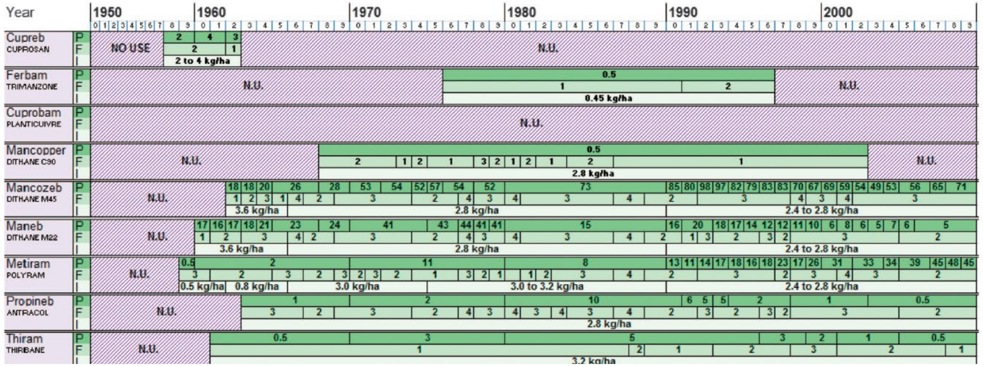
- Chemical specificity
  - Toxicity differs among chemicals in the same class
  - By active ingredient
- Quantitative estimate of exposure
- Intensity of exposure related to tasks, use of PPE, application method
- Mixtures?

Practical Consideration in Exposure Assessment

- Who is exposed (and who to study)?
  - Farmers/farm-owners
    - May know about the pesticides/crops
    - May or may not apply themselves
  - Farmworkers—may be highly exposed
    - Short-term work?
    - Knowledge of pesticides?
  - Regional differences based on specific farm practices
  - Intensity of exposures

Pesticide Exposure Assessment Methods

- Manufacturers
- Crop-Based Exposure Assignment
- Self-report assessment/ questionnaire for individual chemicals



Name of Pesticide	A. Have you ever personally mixed or applied this pesticide?	B. How many years did you personally mix or apply this pesticide?	C. In an average year when you personally used this pesticide, how many days did you it?	D. When did you first personally use this pesticide?
Herbicides *(pesticides used to kill weeds)*				
a. **Aatrex, Atranex** or other ***atrazine*** products	[a_herbicide_cd1] ○ No ↓ ○ Yes →	[a_herbicide_yr1] ○ 1 year or less ○ 2–5 years ○ 6–10 years ○ 11–20 years ○ 21–30 years ○ More than 30 years	[a_herbicide_day1] ○ Less than 5 days ○ 5–9 days ○ 10–19 days ○ 20–39 days ○ 40–59 days ○ 60–150 days ○ More than 150 days	[a_herbicide_fu1] ○ Before 1960 ○ In the 1960s ○ In the 1970s ○ In the 1980s ○ In the 1990s ↓ ○ Mark here if you used this pesticide **last year** [a_herbicide_ls1]

Assessments based on Biological Measurements

- Most pesticides in use today are not persistent
  - Urinary measurements reflect exposure in hours/days
  - Usefulness for cumulative or long-term exposure?
- Exceptions:
  - Organochlorine insecticides
  - Lindane: β-HCH, γ-HCH
  - DDT: *p,p'*-DDE, *p,p'*-DDT
  - Reflect whole body burden

How Can We Study Effects of Pesticides?

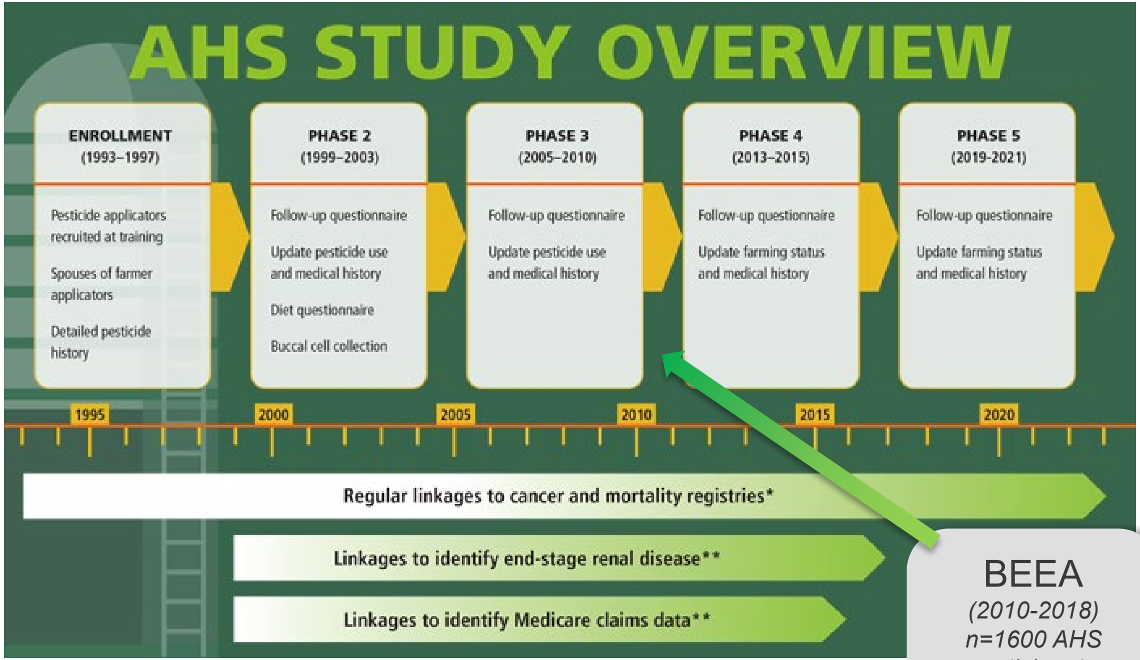
- Need Information on specific active ingredients
- Highly exposed population
- Large population with sufficient follow-up (cohort) or adequate number of exposed cases (case-control)
- Accurate characterization of exposure for exposure-response associations

Agricultural Health Study cohort

Agricultural Health Study

NCI NIEHS EPA NIOSH

- 57,310 licensed pesticide applicators in Iowa and North Carolina (20,518 in NC)
- 32,345 spouses of applicators (10,307 in NC)
- Iowa and North Carolina- diverse agricultural practices



BEEA
(2010-2018)
n=1600 AHS participants
In-person interview, including recent pesticide use

Blood, urine and house dust

www.aghealth.nih.gov

Alvanja et al. EHP. 1996

AHS Exposure Assessment Approach

- Apply questionnaire data on individual active ingredients for etiologic analyses
- Self-report duration and frequency at enrollment
- Self-report use again since enrollment at follow-up
- Applicators provide reliable (Blair 2002) and valid (Hoppin 2002) responses related to pesticide use

Cumulative Exposure

- Phase I – lifetime days of use

Name of Pesticide	A. Have you ever personally mixed or applied this pesticide?	B. How many years did you personally mix or apply this pesticide?	C. In an average year when you personally used this pesticide, how many days did you it?	D. When did you first personally use this pesticide?
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AHS Exposure Metrics used in Health Outcome Analyses

- Ever Use
- Frequency of Use
- Cumulative Exposure (Lifetime days of use)
  - Years * Days/year applied
- Intensity-Adjusted Cumulative Exposure
  - Cumulative Exposure * Intensity Score

Intensity-Adjusted Cumulative Exposure

- Intensity-weighting algorithm
  - Factors that affect exposure
    - Application Method (Apply)
    - Mixing chemicals (Mix)
    - Repair of equipment (Repair)
    - Use of Personal Protective Equipment (PPE)

Intensity Score = (Apply + Mix + Repair) * PPE

(Dosemeci et al., *Ann Occup Hyg*. 2002; Coble et al., *Int J Environ Res Public Health*. 2011)

- Field studies (Hines 2008 et al., Ann Occ Hyg, Thomas et al., JESEE, 2010A, Thomas et al., JESEE, 2010B)

Intensity score * Lifetime Days = **Intensity-weighted Lifetime Days (IWLD)**

Exposure metric comparison

Lifetime number of exposure days	N	RR	95%CI	Intensity-weighted exposure days	N	RR	95%CI
Lung*							
No exposure	199	1.00	Referent	No exposure	199	1.00	Referent
<20	32	1.11	0.75 to 1.65	<368	22	1.09	0.61 to 1.53
20.0–38.8	16	0.76	0.44 to 1.30	369–1800	25	0.99	0.66 to 1.52
>38.8	36	1.60	1.11 to 2.31	>1800	37	1.41	0.98 to 2.04
		P_{trend}=0.02				P_{trend}=0.08	

Jones et al. OEM. 2014

Insecticide-impregnated ear tag on cow

Crop pesticide applicator wearing PPE

AHS Cancer Incidence

Lower overall cancer incidence

- **Reduced cigarette** smoking
- **Increased** physical activity
- Healthy worker effect

Some cancer sites are elevated compared to the general population

Farming exposures may contribute to excess cancer risk

- Pesticides, diesel engine exhaust, UV radiation, bacteria and viruses

Standardized incidence ratio

- $SIR = \frac{\text{Observed number of cases in study population}}{\textbf{Expected number of cases} \text{ in the study population}}$

$$\textbf{Expected number of cases} = \text{person} - \text{years in the study population} \ * \ \text{adjusted cancer rates in reference population}$$

Koutros et al. OEM. 2010, Lerro et al. Cancer Causes & Control. 2019

Cancer incidence in the Agricultural Health Study after 20 years of follow-up among AHS private applicators

	N	SIR	95% CI
All Sites	8256	0.91	0.89, 0.93
Lip	63	2.22	1.71, 2.84
Esophagus	102	0.71	0.58, 0.86
Colon and Rectum	842	0.95	0.89, 1.02
Liver and Bile Duct	78	0.56	0.45, 0.70
Pancreas	183	0.83	0.72, 0.96
Larynx	66	0.48	0.37, 0.62
Lung and Bronchus	807	0.51	0.48, 0.55
Prostate	3169	1.15	1.11, 1.19
Testis	45	1.31	0.96, 1.75
Urinary Bladder	411	0.70	0.63, 0.77
Thyroid	82	1.15	0.92, 1.43
Chronic Lymphocytic Leukemia	166	1.17	1.00, 1.36
Diffuse Large B-Cell Lymphoma	145	1.16	0.98, 1.37
Follicular Lymphoma	81	1.14	0.91, 1.42
Multiple Myeloma	146	1.18	0.99, 1.38
Acute Myeloid/Monocytic Leukemia	86	1.29	1.03, 1.59

Lerro et al. Cancer Causes & Control. 2019

Cancer incidence in the Agricultural Health Study after 20 years of follow-up among AHS spouses

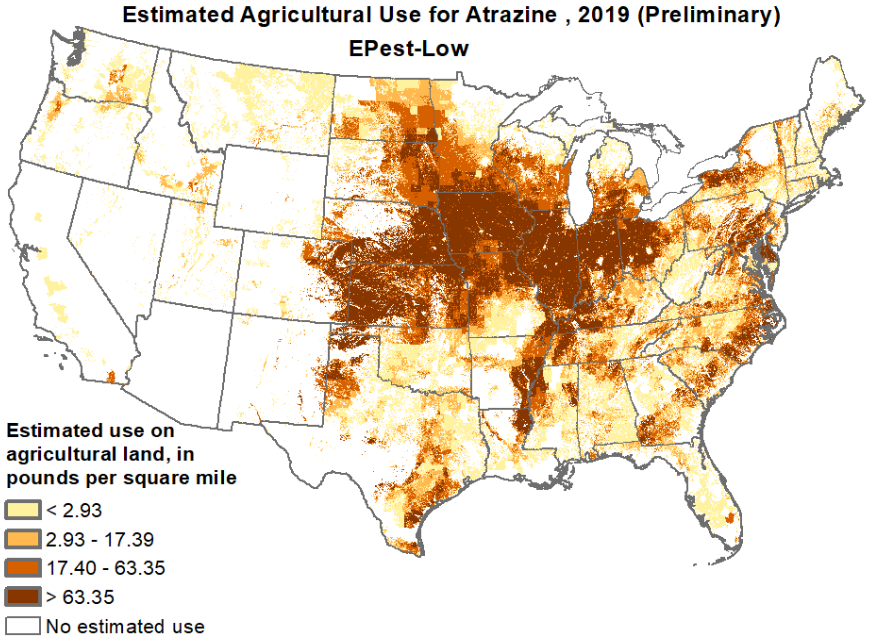
	N	SIR	95% CI
All Sites	3720	0.89	0.86, 0.92
Esophagus	9	0.51	0.23, 0.97
Colon and Rectum	346	0.87	0.78, 0.96
Pancreas	71	0.69	0.54, 0.87
Peritoneum	21	1.80	1.11, 2.75
Lung and Bronchus	252	0.41	0.36, 0.46
Melanoma of the Skin	177	1.21	1.04, 1.40
Breast	1389	1.05	0.99, 1.11
Cervix Uteri	29	0.50	0.34, 0.72
Corpus and Uterus	323	1.13	1.01, 1.27
Ovary and Fallopian Tube	122	0.87	0.72, 1.04
Thyroid	118	1.20	0.99, 1.44
Chronic Lymphocytic Leukemia	43	0.88	0.63, 1.18
Diffuse Large B-Cell Lymphoma	70	1.23	0.96, 1.55
Marginal Zone Lymphoma	25	1.46	0.95, 2.16
Follicular Lymphoma	54	1.33	1.00, 1.74
Acute Myeloid/Monocytic Leukemia	33	1.21	0.83, 1.69

Lerro et al. Cancer Causes & Control. 2019

Pesticide-cancer risk analysis: Atrazine

Atrazine

- Second most applied herbicide in the US
- Commonly applied on corn, sorghum, and sugar cane
- Water soluble and persistent
  - Prevalent contaminant in soil and water
- Known endocrine disruptor
- Currently banned in the European Union (EU)



US Geological Survey. National Water-Quality Assessment (NAWQA) & Pesticide National Synthesis Project.

Atrazine cancer epidemiology

- Few epidemiologic studies
- Suggestive associations with:
  - Prostate (MacLennan et al. *J Occup Environ Med.* 2002)
  - Non-Hodgkin's lymphoma (Schroeder, et al. *Epi*. 2001, De Roos et al. *Occup Environ Med*. 2003)
  - Kidney (Andreotti et al. *EHP*. 2020)
  - Other sites (e.g., stomach, ovarian, pediatric cancers)
- Heterogeneity in study design, exposure assessment, and power
- Last comprehensive cancer epidemiological study focused on occupational exposures among farmers conducted in 2011, *n=3,146* (Beane Freeman et al. *EHP*. 2011)

Re-examine the association between **occupational atrazine use** and cancer risk within the AHS cohort

- 6,631 exposed cancer cases- a **two-fold increase** since the 2011 study
- Updated cumulative exposures

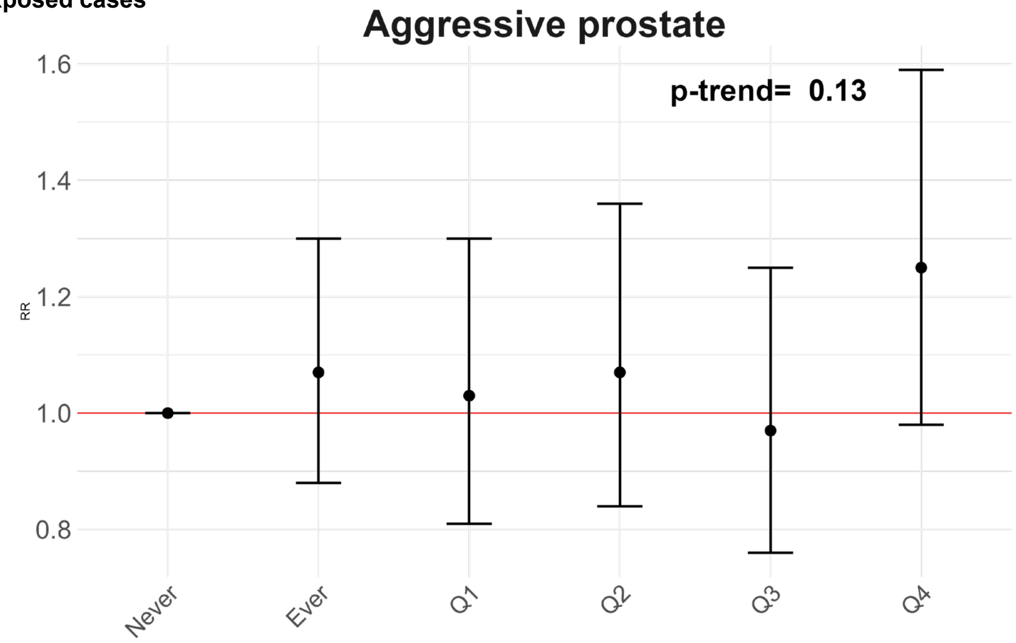
Unlagged Atrazine Use and Risk of **Lung Cancer** in AHS Applicators

Remigio et al.. In revision

Adjusted for age, state, education, smoking, alcohol, family history of cancer, alachlor, metolachlor, trifluralin and 2,4-D

Unlagged Atrazine Use and Risk of **Aggressive Prostate Cancer** in AHS Applicators

n=558 exposed cases

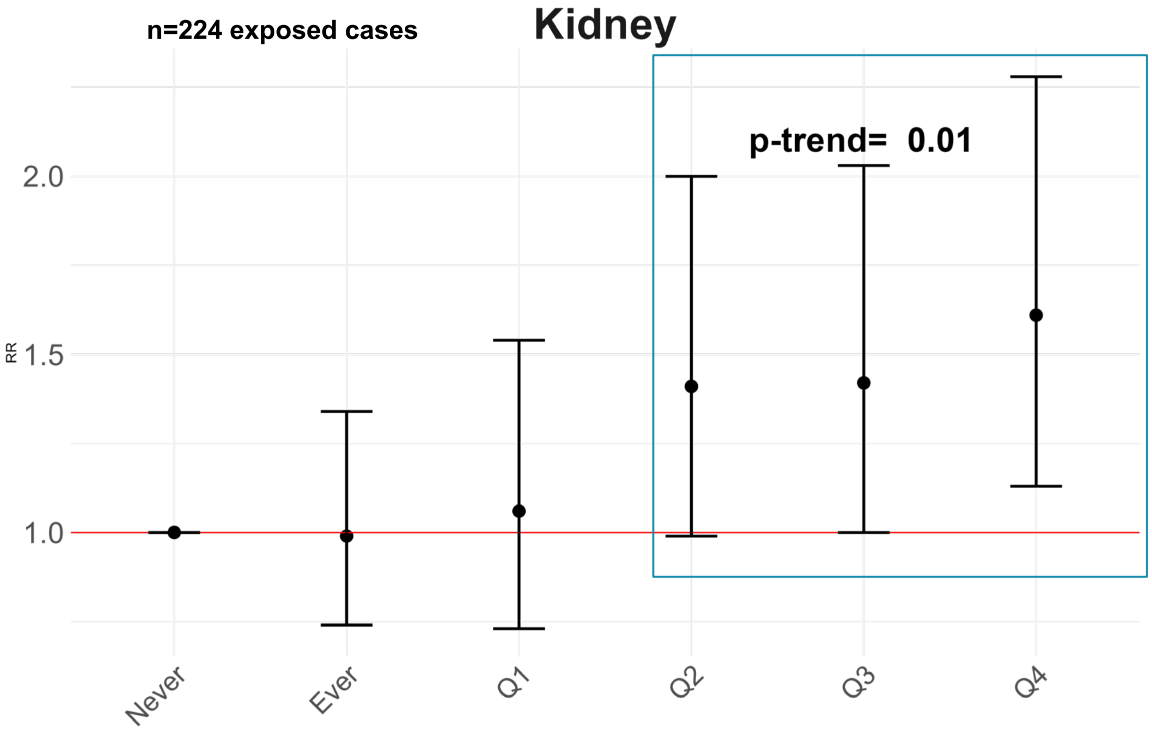


Aggressive prostate cancer ~ Gleason score at or above 8 | Grade or stage at or above 3 | Prostate cancer as cause of death

Remigio et al.. In revision

Adjusted for age, state, education, smoking, alcohol, family history of cancer, alachlor, metolachlor, trifluralin and 2,4-D

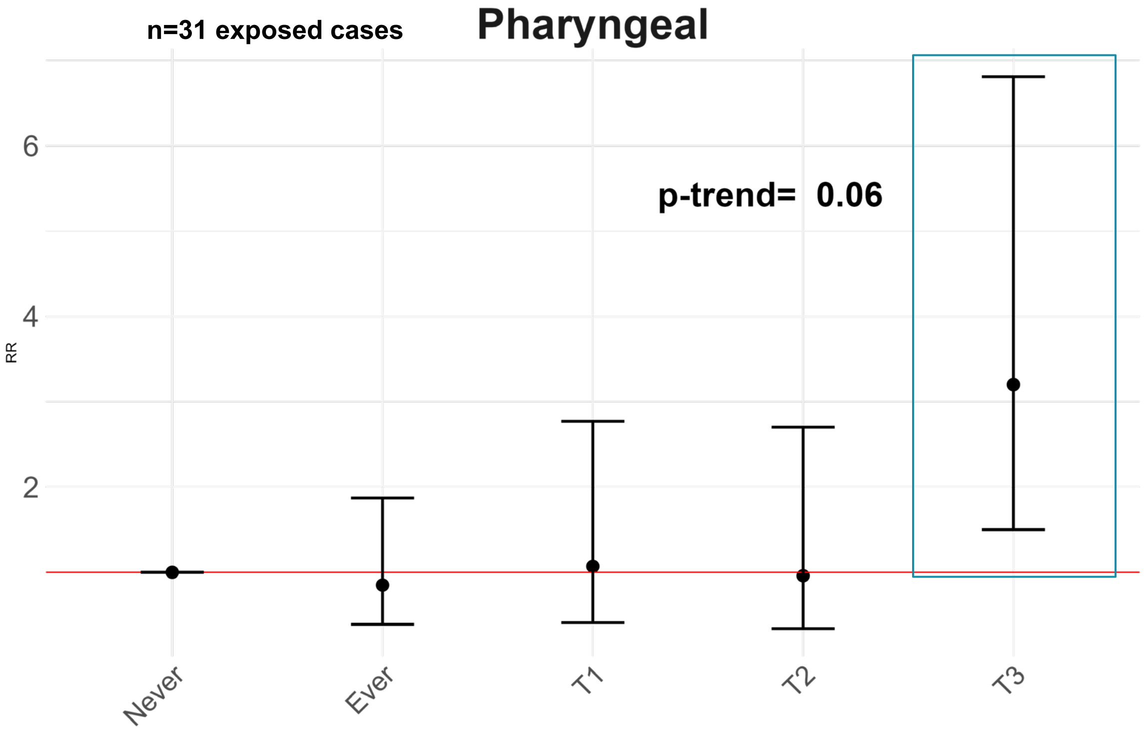
25-year Lagged Atrazine Use and Risk of **Kidney Cancer** in AHS Applicators



Remigio et al.. In revision

Adjusted for age, state, education, smoking, alcohol, family history of cancer, alachlor, metolachlor, trifluralin and 2,4-D

25-year Lagged Atrazine Use and Risk of **Pharyngeal Cancer** in AHS Applicators



Remigio et al.. In revision

Adjusted for age, state, education, smoking, alcohol, family history of cancer, alachlor, metolachlor, trifluralin and 2,4-D

More Results

- Additional suggestive increased risk by age groups
    - Below 50 years: NHL (ever), and significant p-trends with subtypes (Mature B-cell lymphoma)
    - Below 60 years: aggressive prostate (p-trend=0.001, p-interaction=0.0005)
    - 70 and older: esophageal (ever)
- No meaningful associations were found in other sites

Evidence of biological plausibility from Corn Farmer Study

- Atrazine exposure can influence oxidative stress (a key characteristic of a carcinogen)
- A molecular epidemiologic study found a short-term relationship between atrazine exposure and 8-hydroxy-2'-deoxyguanosine (8-OhdG) in analyses restricted to individuals with measures of atrazine mercapturate above the detection limit

Lerro et al., Environ Mol Mutagen. 2017

Pesticides and Cancer

- Pesticide use and lung cancer risk (Bonner et al., EHP 2017)
- Insecticide use and breast cancer in AHS spouses (Engel et al., EHP 2017)
- Alachlor use and cancer incidence (Lerro et al., JNCI 2018)
- Glyphosate use and cancer incidence (Andreotti et al., JNCI 2018)
- Organochlorines and cancer risk in AHS spouses (Louis et al., Environ Health 2018)
- Pesticide use and aggressive prostate cancer (Pardo et al., 2020)
- Pesticide use and breast cancer among AHS spouses (Werder et al., Environ Health 2020)
- Pesticide use and kidney cancer (Andreotti et al., Environ Epi 2020)
- Dicamba use and cancer incidence (Lerro et al., Int J Epi 2021)
- Pesticide use and thyroid cancer among AHS males (Lerro et al. Environ Intl 2021)
- Pesticide use and MGUS (Hofmann et al., EHP 2021)

Pesticides and Other Outcomes

- Thyroid disease
- Allergic and non-allergic wheeze
- Olfactory impairment
- Rheumatoid arthritis
- Parkinson’s Disease
- Sleep Apnea
- Shingles

AHS data contributed to more than 139 publications in last 5 years; 382 since 1996

Learned Lessons

- Data and work behind estimating long-term exposures
- Quality results dependent on quality data (lines of evidence)
  - Feeds into weight of evidence approaches for determining risk
- New methodologies are out there: Mixtures

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For More AHS Information:

www.aghealth.nih.gov