

Pesticide Exposure Assessment Methodological Issues in Epidemiologic Studies of Childhood Leukemia

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Pesticides in the Environment

- Poisonous substances **intentionally** disseminated in the environment (-*cide*)
- Many have acute and/or chronic human toxicity; some listed as known
  - neurotoxins
  - developmental toxins
  - carcinogens
  - endocrine disruptors
  - immuno-suppressants
- Involuntary exposures in variety of settings



Sources of Pesticide Exposure for Pregnant Women and Children

- Dietary contaminants (ubiquitous)
  - 1996 Food Quality Protection Act; NHANES biomonitoring
- Home indoor and gardening/lawn use
  - 85% of US households store at least 1 pesticide for home use [Adgate 2000]
- Residential proximity to applications (e.g. agricultural)
  - agricultural chemicals detected inside residences and near crops
    - drift from application site
    - take home contamination by farm-workers

Pesticides and Childhood Cancers

Childhood cancers are a rare disease;

- poor statistical power in small studies

Need for

- large and/or highly/widely exposed study populations
- cancer registries



Sources of Pesticide Exposure

- Occupational
  - Production worker
    - e.g. di-bromo-chloro-propane exposure and male sterility
  - Farmers and professional pesticide applicators
    - e.g. used for acute effect studies, also now AHS
- Epidemiology works well in high-dose environments i.e. well-characterized occupational exposures
  - However, for childhood cancers the most important exposures to assess are ubiquitous environmental level exposures to pregnant women and in early childhood

Types of Pesticide Exposures

Dose

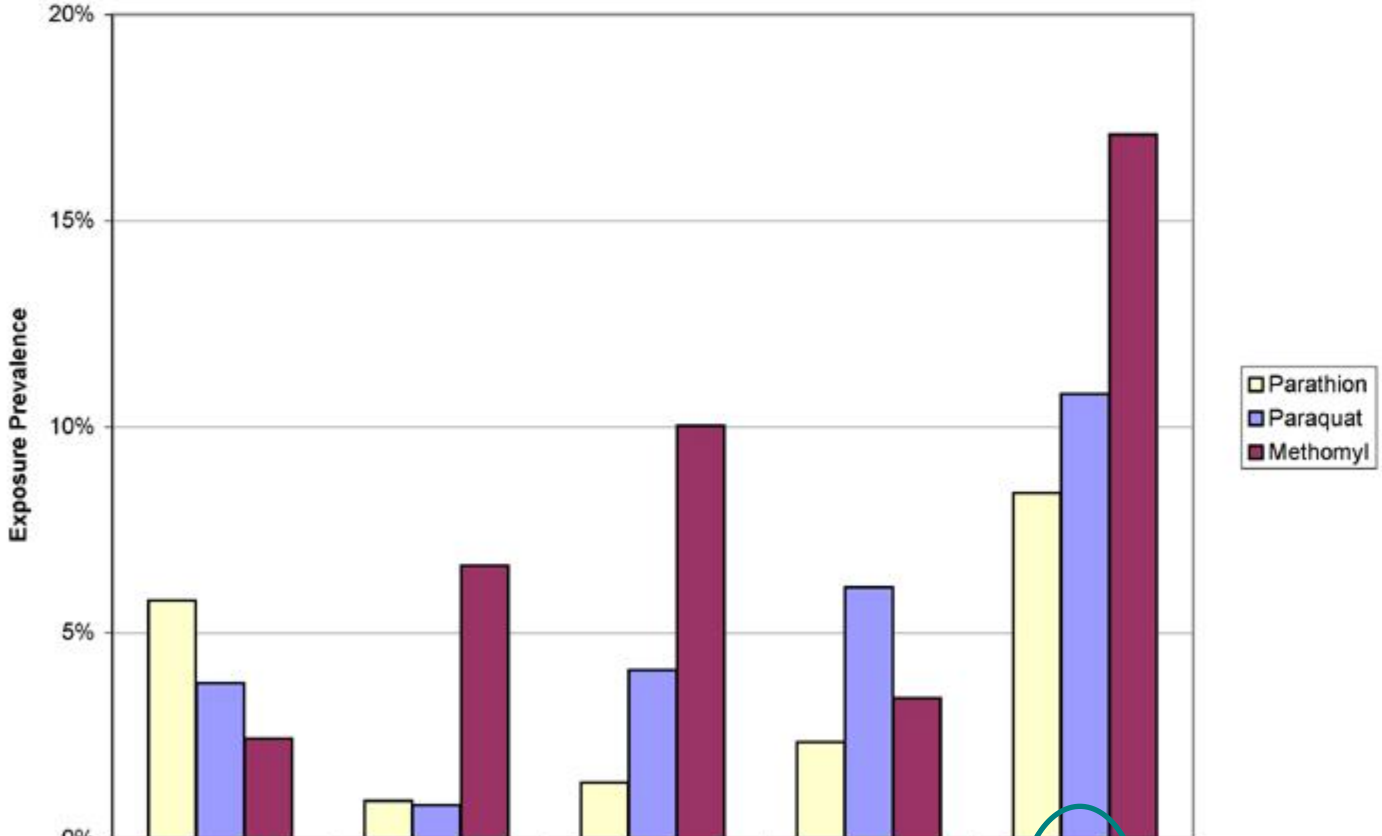
- higher doses may lead to spontaneous abortions or other adverse/competing outcomes?

Need to distinguish

- Maternal, paternal and/or child exposures

- Timing of exposure with respect to sensitive period
  - semen (paternal),
  - prenatal,
  - early infancy etc

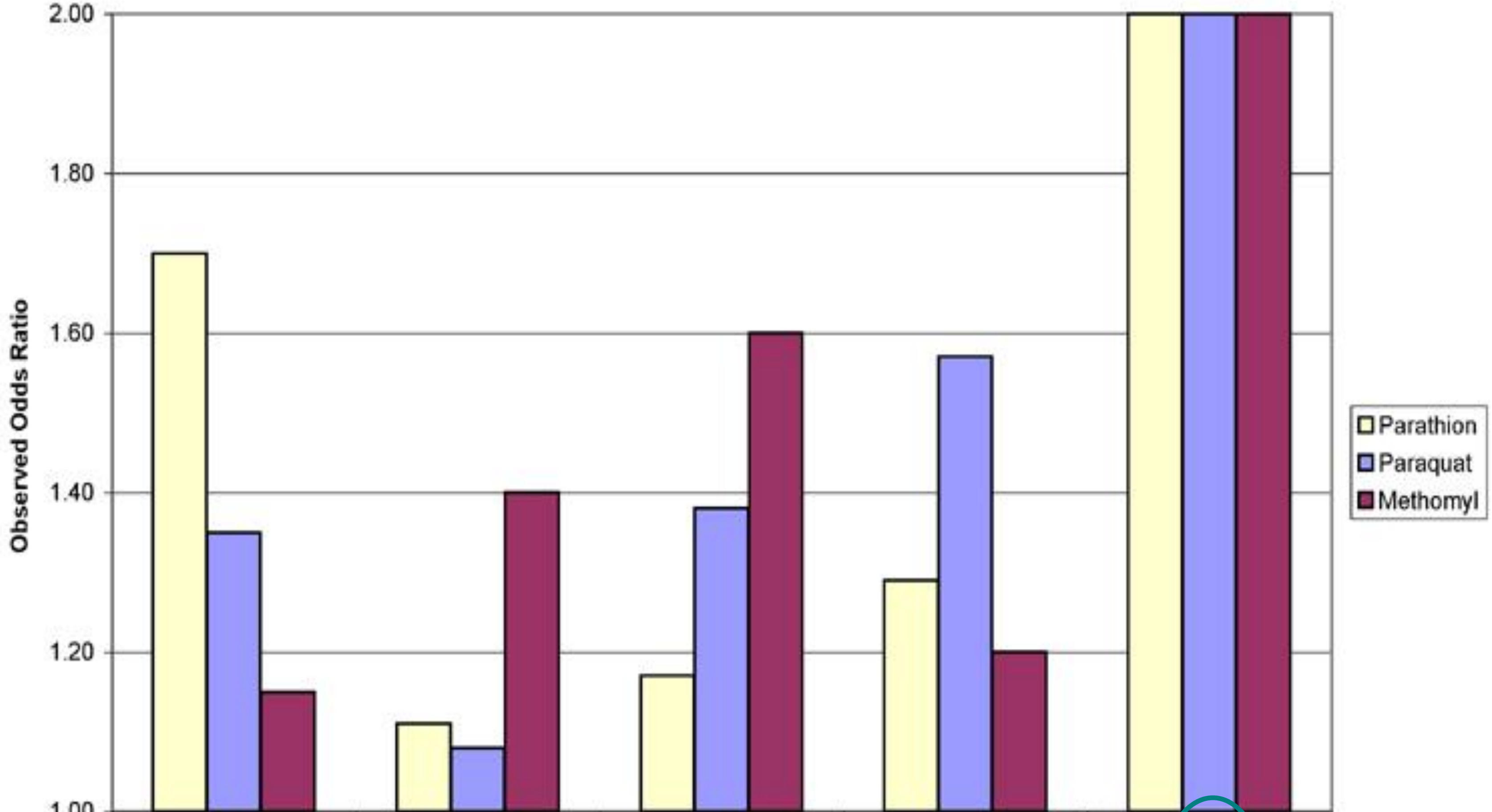
Temporal Differences in Agricultural Pesticide Applications within 500m of Residences in Central CA



	Winter	Spring	Summer	Autumn	Annual
Parathion	5.8%	0.9%	1.4%	2.4%	8.4%
Paraquat	3.8%	0.8%	4.1%	6.1%	10.8%
Methomyl	2.4%	6.6%	10.0%	3.4%	17.1%

Rull R, Ritz B. Historical Pesticide Exposure In California Using Pesticide Use Reports And Land-Use Surveys: An **Assessment Of Misclassification Error And Bias.** EHP 2003;111(13):1582-9.

Exposure Misclassification for hypothetical **true OR=2** when using annual averages instead of seasonal exposures for sensitive windows



	Winter	Spring	Summer	Autumn	True OR
Parathion	1.70	1.11	1.17	1.29	2
Paraquat	1.35	1.08	1.38	1.57	2
Methomyl	1.15	1.40	1.60	1.20	2

Rull R, Ritz B. Historical Pesticide Exposure In California Using Pesticide Use Reports And Land-Use Surveys: An **Assessment Of Misclassification Error And Bias**. EHP 2003;111(13):1582-9.

Exposures Assessment Pesticides in Childhood Cancer Studies

Studies relied on self-reports of

- occupational or
- home and gardening pesticide use by pare
  - Poor/limited recall and reporting of specific products

Self-reported exposures often cannot be validated and recall bias never be ruled out!

Example: ORs (95% CI)[2] for self-reported and land-use-map-based proximity (0.25- mile) to any or specific agricultural crops and NTD in CA 1987-88

Crop Type	Self-Reported	Map-Based
Any Crops	1.6 (1.1, 2.5)	1.2 (0.8, 1.7)
Any non-permanent crops	1.4 (0.9, 2.3)	1.1 (0.7, 1.7)
Any orchards	2.0 (1.2, 3.4)	1.1 (0.7, 2.0)
Deciduous orchards	2.2 (1.1, 4.3)	1.3 (0.7, 2.4)
Subtropical/citrus orchards	2.1 (0.9, 4.8)	0.7 (0.3, 1.8)
Vineyards	1.1 (0.5, 2.5)	2.5 (1.1, 5.6)

[2] ORs adjusted for maternal ethnicity, education, geographic region, and gestational cigarette smoking and vitamin use.

Rull RP, Ritz B, Shaw GM. Validation of self-reported proximity to agricultural crops in a case–control study of neural tube defects. *J Expo Sci Environ Epidemiol. 2006 Mar;16(2):147-55.*

	Model 1	**Model 2**
Outcome	Underreporting Proximity	Overreporting Proximity
Study Population (by map-based proximity)	Lived within ¼-mile of crops	Did not live within ¼-mile of crops
Predictor	OR (95% CI)	OR (95% CI)
NTD Case vs. Control	0.5 (0.3, 1.1)	1.3 (0.7, 2.6)
Rural vs. Urban residence	0.6 (0.3, 1.3)	2.1 (1.0, 4.1)
Central vs. Southern California	0.4 (0.2, 1.0)	2.3 (1.1, 4.7)
Employed vs. Unemployed	2.3 (1.2, 4.4)	1.2 (0.6, 2.3)
No college vs. Any college	1.3 (0.6, 3.0)	0.4 (0.2, 0.9)
[3] No observed associations for maternal ethnicity, age, or gestational smoking.		

Rull RP, Ritz B, Shaw GM. Validation of self-reported proximity to agricultural crops in a case–control study of neural tube defects. *J Expo Sci Environ Epidemiol. 2006 Mar;16(2):147-55.*

Personal-monitoring or Biomarker Data for Pesticides

- collection and/or analysis are expensive
- need to be planned/done prospectively

thus, mostly lacking

- Case-control study: exposure assessment is *ex post facto*
- Cohort studies:
  - sample during relevant periods of exposure
    - Biomarkers for some pesticides are very transient i.e. short physiologic half-life
  - For storing samples need to choose matrix and methods carefully
    - Blood Urine, meconium, amniotic fluid (hair, nail)
    - Inter-individual differences in metabolism, feasibility of collection



Personal-monitoring/ Biomarker Data: Pesticides in Pregnancy

- Berkowitz et al 2003
  - 386 pregnant women in New York
  - Urine sample : metabolites for pyrethroids (95% pos), pentachlorophenol (94% pos), chlorpyrifos (80% pos)
- Whyatt &Perera et al. 2003
  - ~400 women in Washington Heights New York
  - Dust and (personal) air samples, umbilical cord blood
    - Chlorpyrifos
- Bradman & Eskenazi et al. 2001-2005
  - ~600 pregnant women in Salinas Valley CA
  - [smaller pilot: Infant meconium, amniotic fluid]
  - Maternal and cord blood
  - Urine samples: OP metabolites - di-alkyl-phosphates
    - 88-100% positive, only 5% home use, mostly agricultural exposures



Personal-monitoring or Biomarker Data for Pesticides in Children

- Fenske & Needham et al. since 1990
  - Preschoolers in Seattle: parental garden use of pesticides predicted OP metabolite levels in children
  - 109 children ages 6 and younger from Central Washington State agricultural families
    - OP pesticides in soil and dust, handwipe, surface wipe
    - OP (chlorpyrifos and parathion) urinary metabolites in children

- Ag-health (AHS) substudies, Curwin et since 2000
  - 107 farm and non-farm children (and parents) in Iowa, 2 urine samples and home dust samples
    - Chlorpyrifos, atrazine, glyphosate urinary metabolites in children
    - Parental and child exposures correlated well within families

Types of Pesticide Exposures

Distinguish type of pesticide

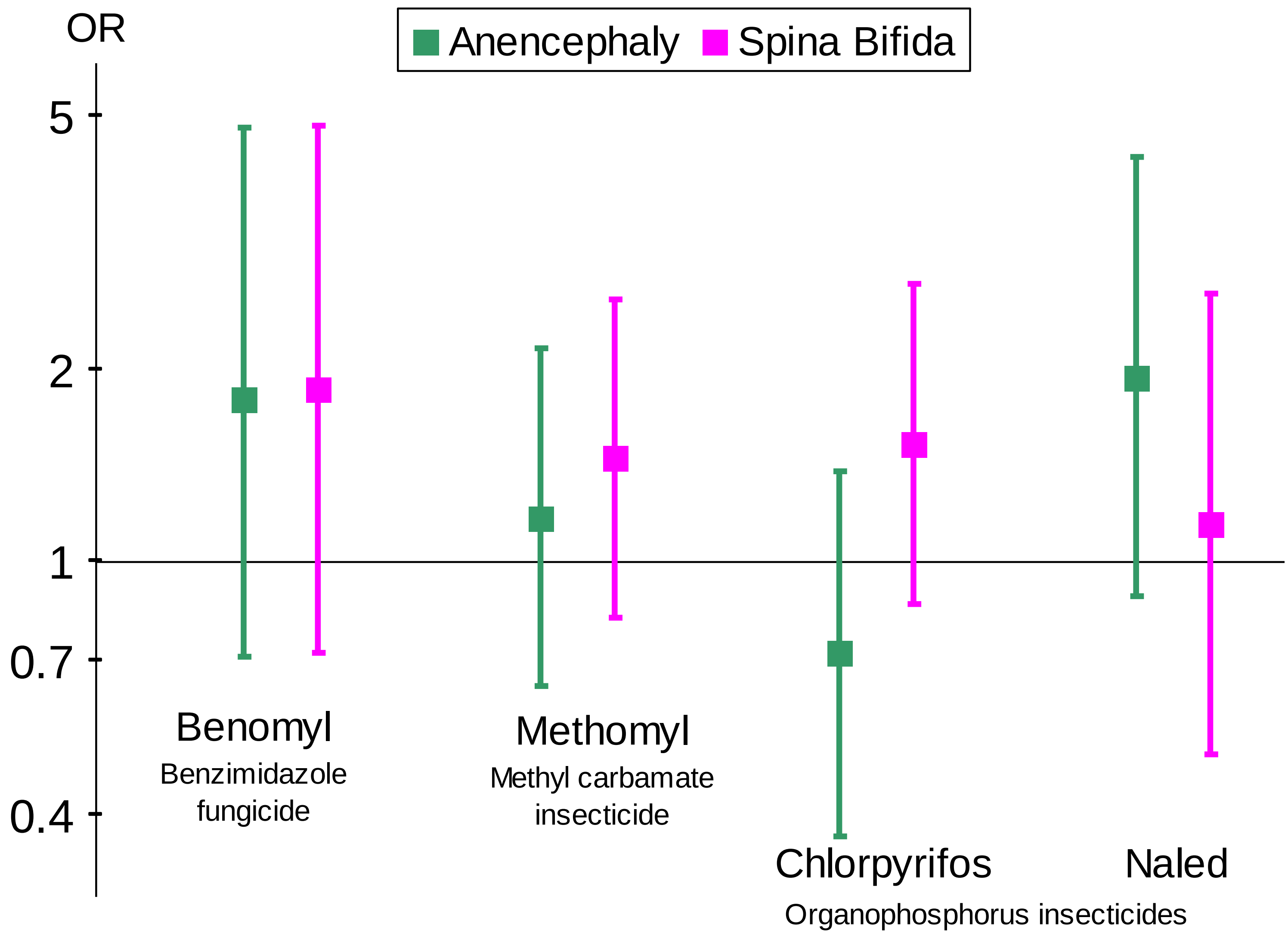
- Use type:
  - fungicide, insecticide, herbicide etc.

- Chemical class:
  - organochlorine, organophosphate, carbamate, pyrethroid etc

- Type of function in presumed pathophysiologic pathways:
  - DNA damage
  - immunotoxic
  - endocrine disrupting
  - cholinesterase inhibition
  - microtubule disrupting
  - proteasome or mitochondrial inhibition etc.

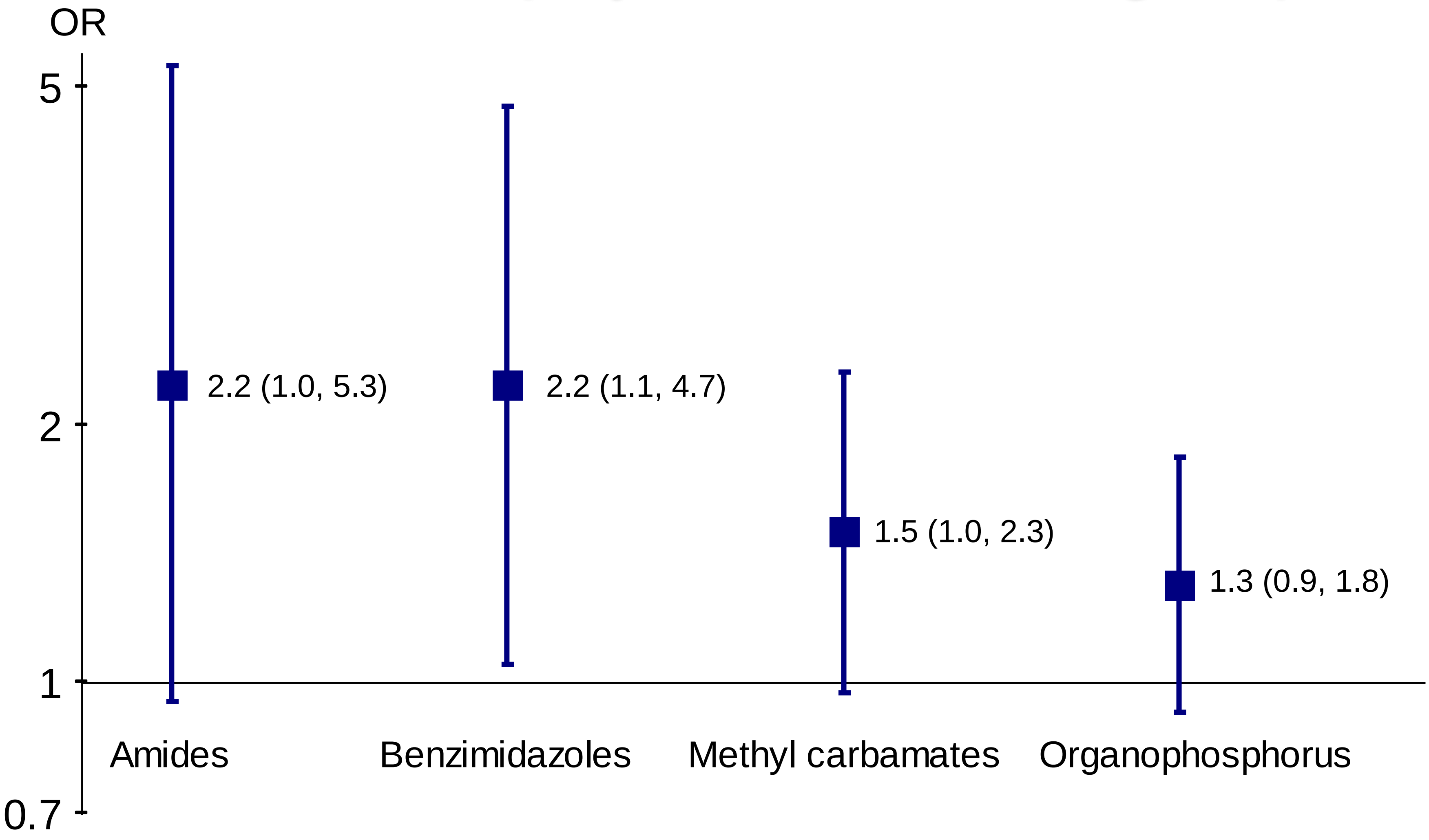
Rull RP, Ritz B, Shaw GM. Neural Tube Defects And Maternal Residential Proximity To Agricultural Pesticide Applications. Am J Epidemiol. 2006 Apr 15;163(8):743-53.

Specific Pesticides (59 investigated) by Disease Subtype



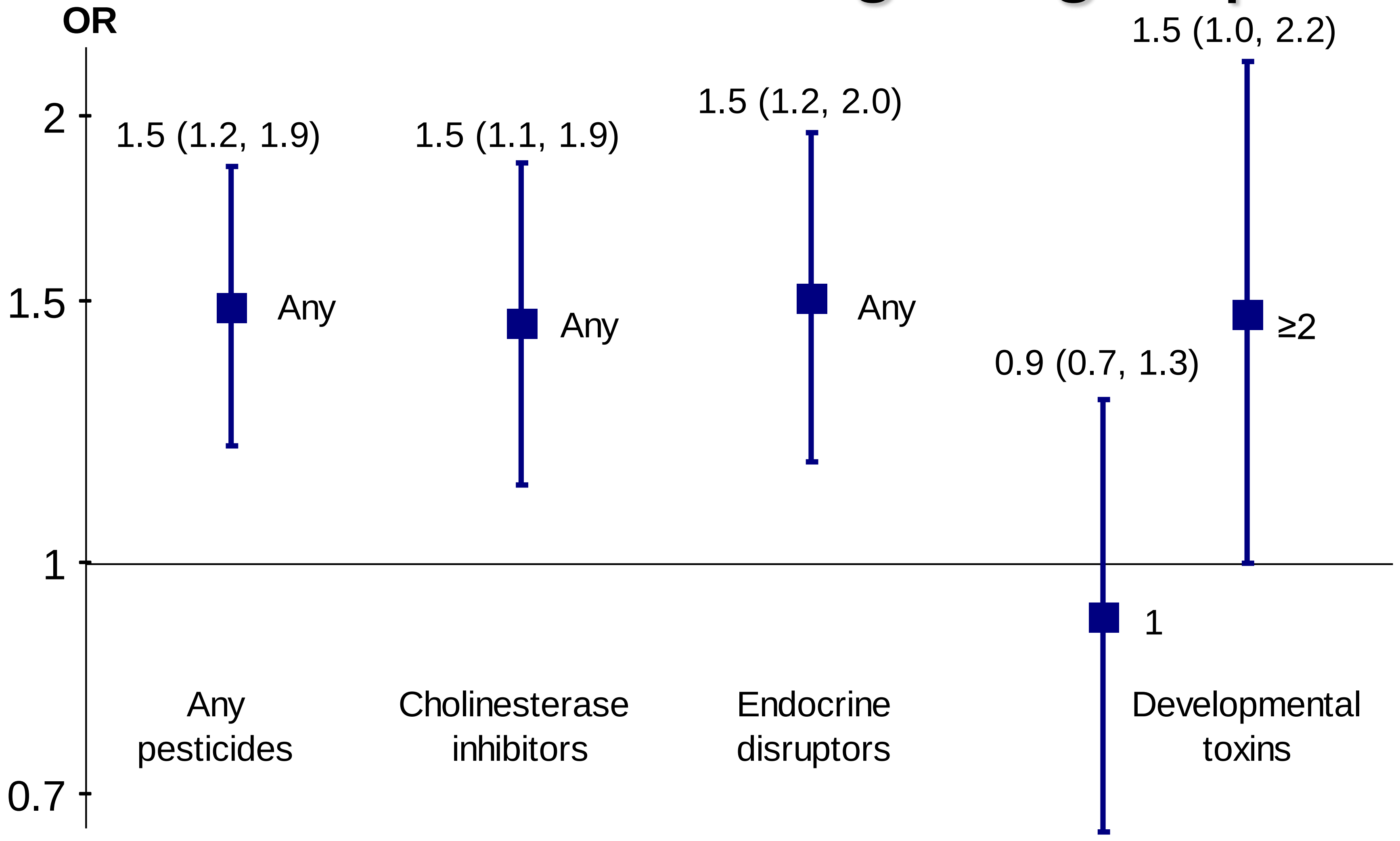
Rull RP, Ritz B, Shaw GM. Neural Tube Defects And Maternal Residential Proximity To Agricultural Pesticide Applications. Am J Epidemiol. 2006 Apr 15;163(8):743-53.

NTD results: physicochemical groups



Rull RP, Ritz B, Shaw GM. Neural Tube Defects And Maternal Residential Proximity To Agricultural Pesticide Applications. Am J Epidemiol. 2006 Apr 15;163(8):743-53.

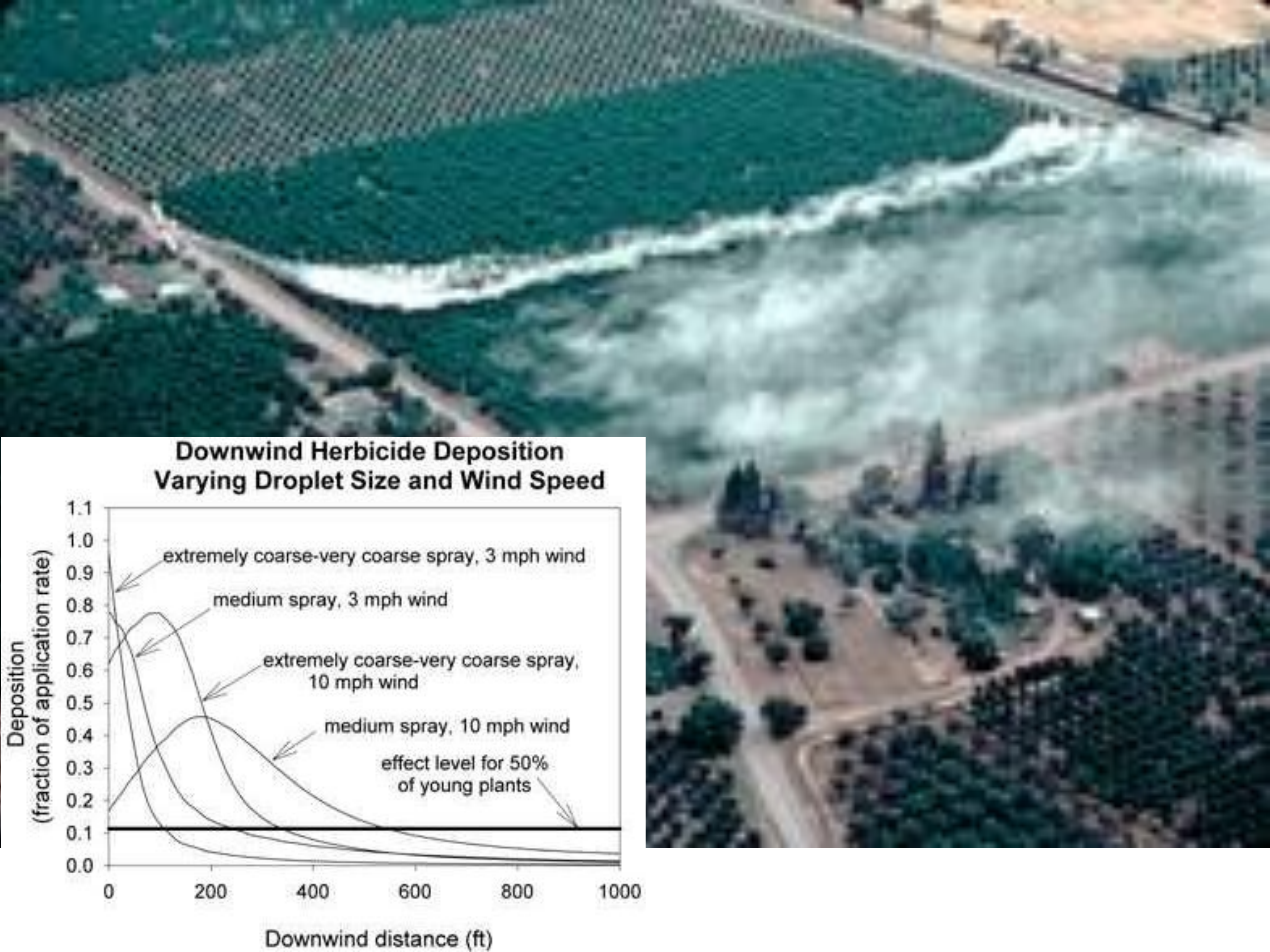
NTD results: toxicological groups



Exposures Assessment Pesticides in Childhood Cancer Studies

– broad regional indicators of pesticide use (ecologic studies) for proximity to agricultural activities

Why is ambient exposure important?

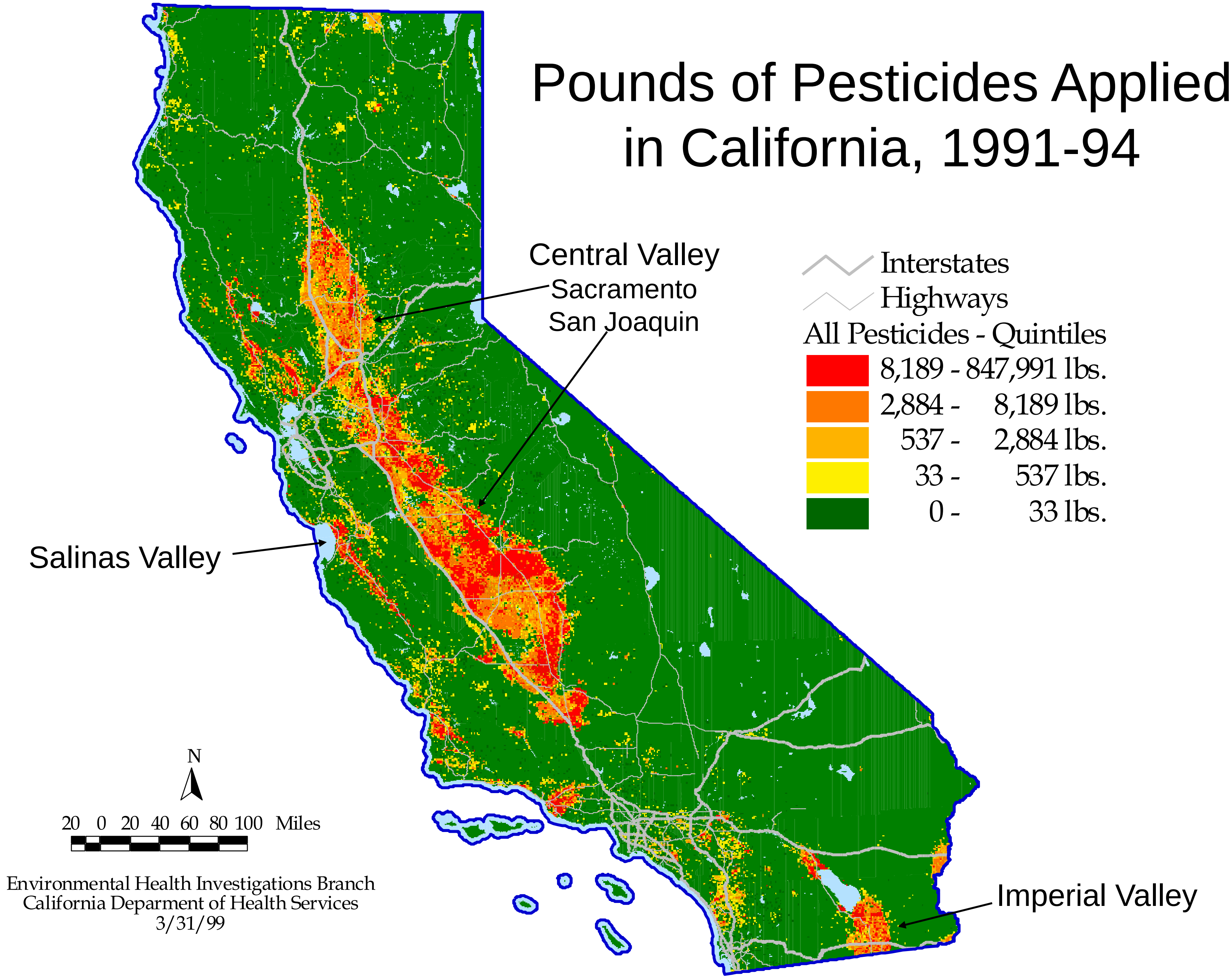

Downwind Herbicide Deposition
Varying Droplet Size and Wind Speed
extremely coarse-very coarse spray, 3 mph wind
medium spray, 3 mph wind
extremely coarse-very coarse spray,
10 mph wind
medium spray, 10 mph wind
effect level for 50%
of young plants
Deposition
(fraction of application rate)
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
200
400
600
800
1000
Downwind distance (ft)

California Environmental Protection Agency

Air Resources Board

Ambient Air Monitoring for Methyl Bromide and 1,3-Dichloropropene in Kern County – Summer 2001

Concentrations of methyl bromide were measured as high as 98.3 micrograms per cubic meter of sampled air ($\mu g/m^3$) at the University of California's Cotton Research Station (CRS) near the town of Shafter. Methyl bromide was used north and northwest of the CRS site associated with growing roses. The prevailing wind in the CRS area is from the northwest. No methyl bromide was used at the CRS during 2001. The highest average concentration for the 8-week canister monitoring period was 11 $\mu g/m^3$, also measured at the CRS site. Of the 198 ambient canister samples, 171 contained concentrations of methyl bromide above the estimated quantitation limit (reporting limit) of 0.036 $\mu g/m^3$, and 27 samples were invalidated due to a sampling problem.



Pounds of Pesticides Applied in California, 1991-94
Central Valley
Sacramento
San Joaquin
Salinas Valley
Imperial Valley
Interstates
Highways
All Pesticides - Quintiles
8,189 - 847,991 lbs.
2,884 - 8,189 lbs.
537 - 2,884 lbs.
33 - 537 lbs.
0 - 33 lbs.
N
20 0 20 40 60 80 100 Miles
Environmental Health Investigations Branch
California Deparment of Health Services
3/31/99



Pesticide Use Reporting in California

- California: most agriculturally productive state in US
- Since 1972, required filing of pesticide use reports (PUR) of commercial applications
  - Department of Pesticide Regulation
- For each application, detailed reporting of:
  - Active pesticide ingredient and pounds applied
  - Crop & the number of treated acres
  - Location (township-range sections; area ≈ 1 sq. mi.)
  - Date of application

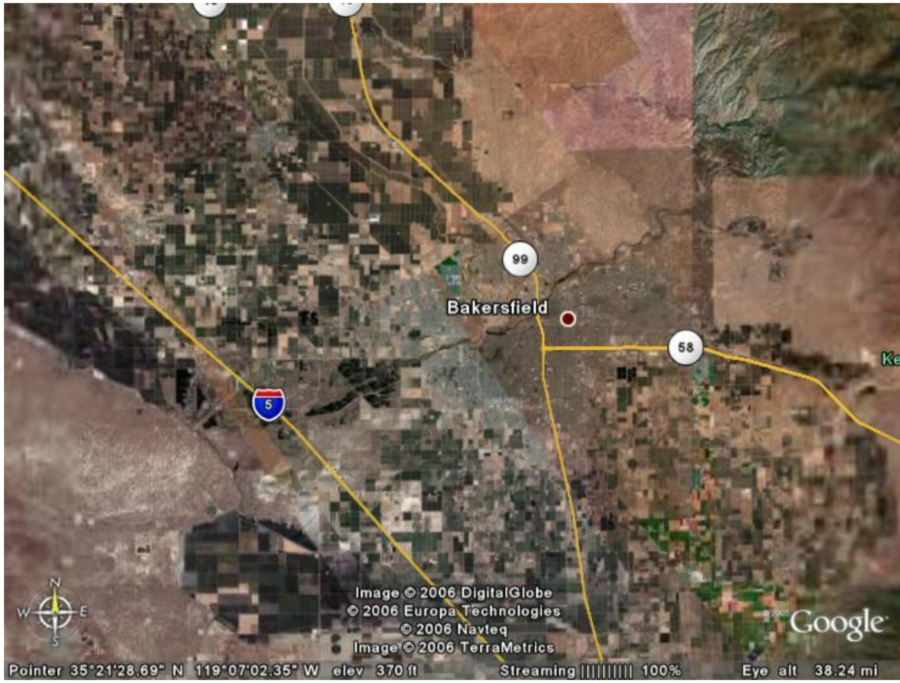


Pesticide Use Report Data

- County: Kern
- Location: 15M28S27E19
- Application date: 2/23/1989
- Commodity: 2503 (Grapes)
- Method: Ground
- Treated: 424 acres
- Product applied: 155 gallons
- Chemical: 00459 (Parathion)
- Percentage: 80%
- Active Ingredient Pounds: 1,241

Exposures to Agricultural Pesticides in California

Aerial photo Kern County 1953



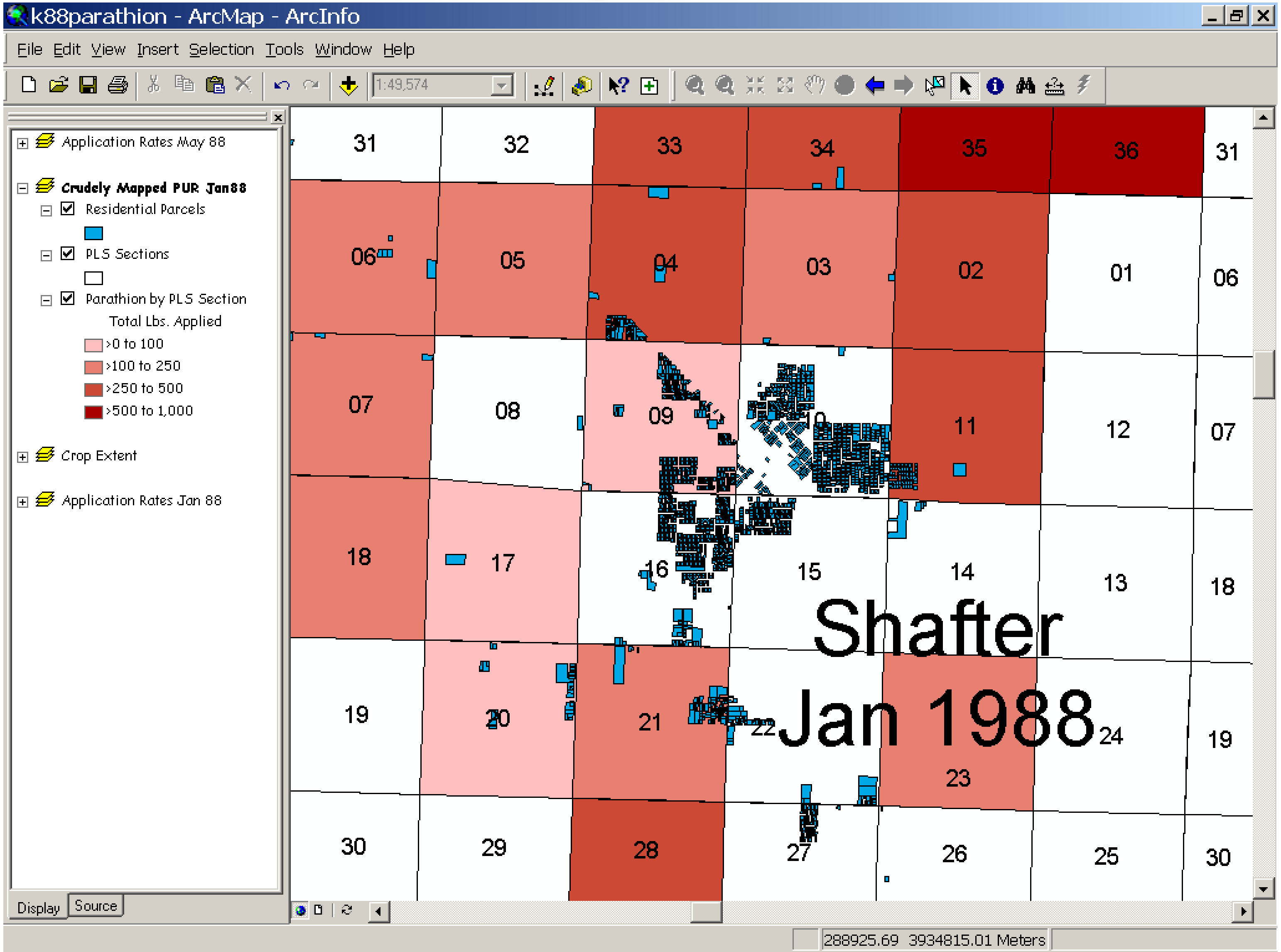
Google earth image, Bakersfield
Kern County 2007

Geocoding

All address/locations automatically & manually geocoded (GoogleEarth)

<address>336 Lloyd St, Bakersfield, CA 93307, USA</address>
<LookAt>
<longitude>-119.0010070800781</longitude>
<latitude>35.3549385070217 9</latitude>

Mapping pesticide



Exposure Misclassification for hypothetical **true OR=2** when using broad or narrow pesticide exposure classifications

Table 4. Matrix of simulated OR estimates (percent attenuation) based on a true OR and the prevalence, sensitivity, and specificity estimates presented in Table 3.

	True OR = 1.5		True OR = 2		True OR = 3	
Pesticide	Narrow	Broad	Narrow	Broad	Narrow	Broad
Methomyl	1.37 (26)	1.18 (64)	1.70 (30)	1.35 (65)	2.27 (37)	1.70 (65)
Paraquat	1.38 (24)	1.15 (70)	1.73 (27)	1.30 (70)	2.36 (32)	1.60 (70)
Parathion	1.35 (30)	1.15 (70)	1.69 (31)	1.31 (69)	2.32 (34)	1.62 (69)
Endosulfan	1.33 (34)	1.11 (78)	1.66 (34)	1.22 (78)	2.27 (37)	1.44 (78)
Maneb	1.23 (54)	1.06 (88)	1.45 (55)	1.12 (88)	1.89 (56)	1.25 (88)

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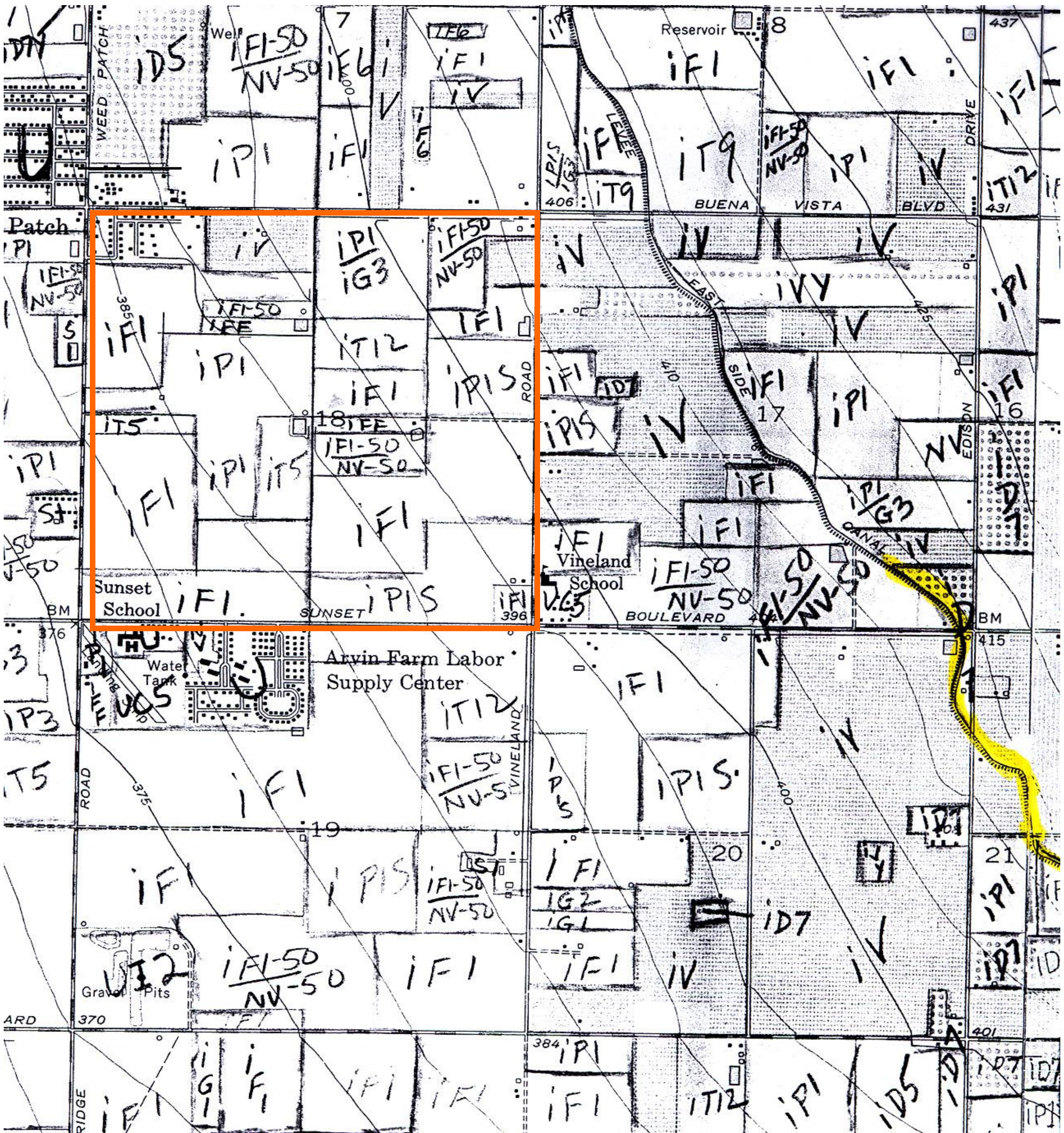
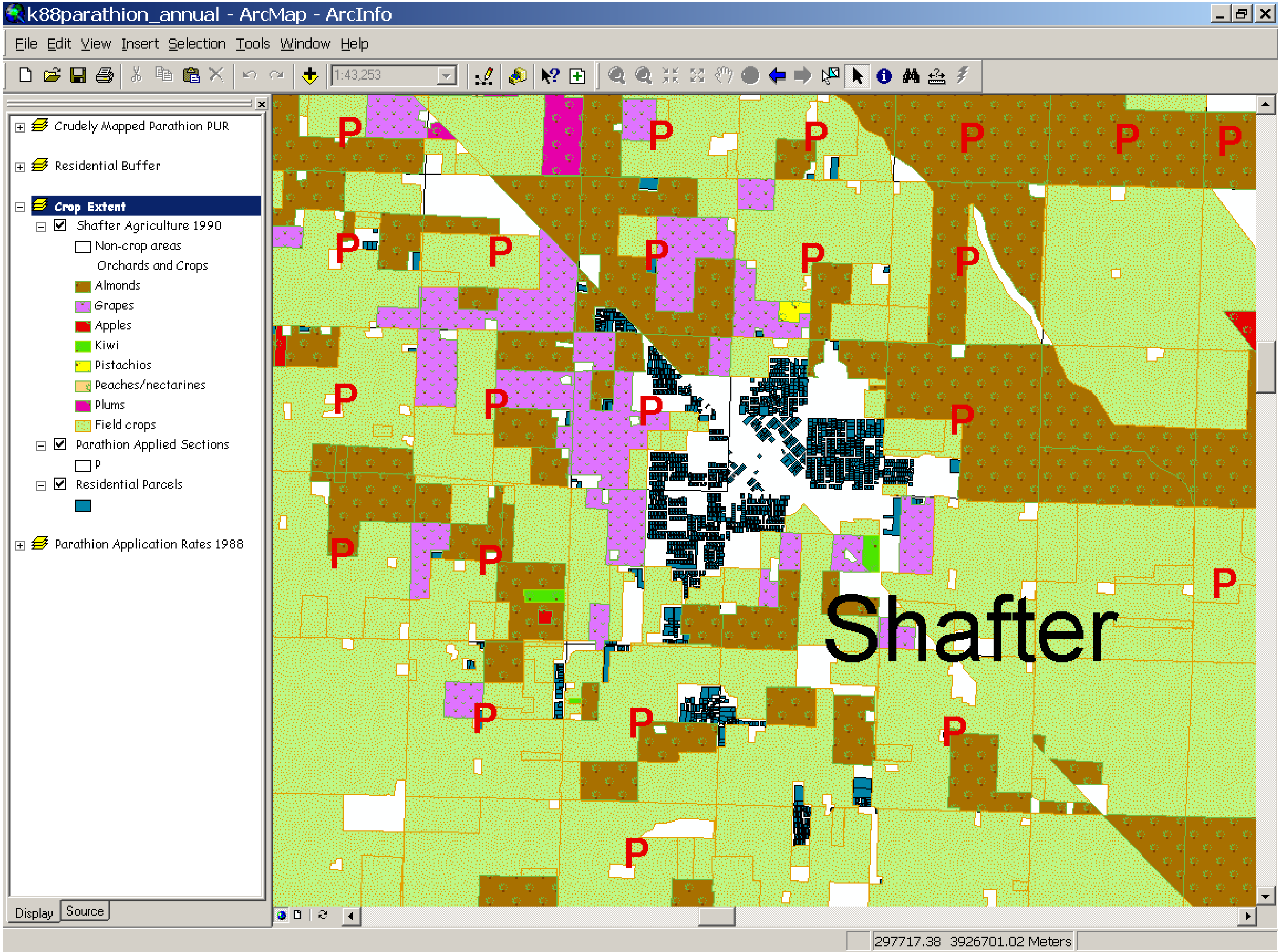
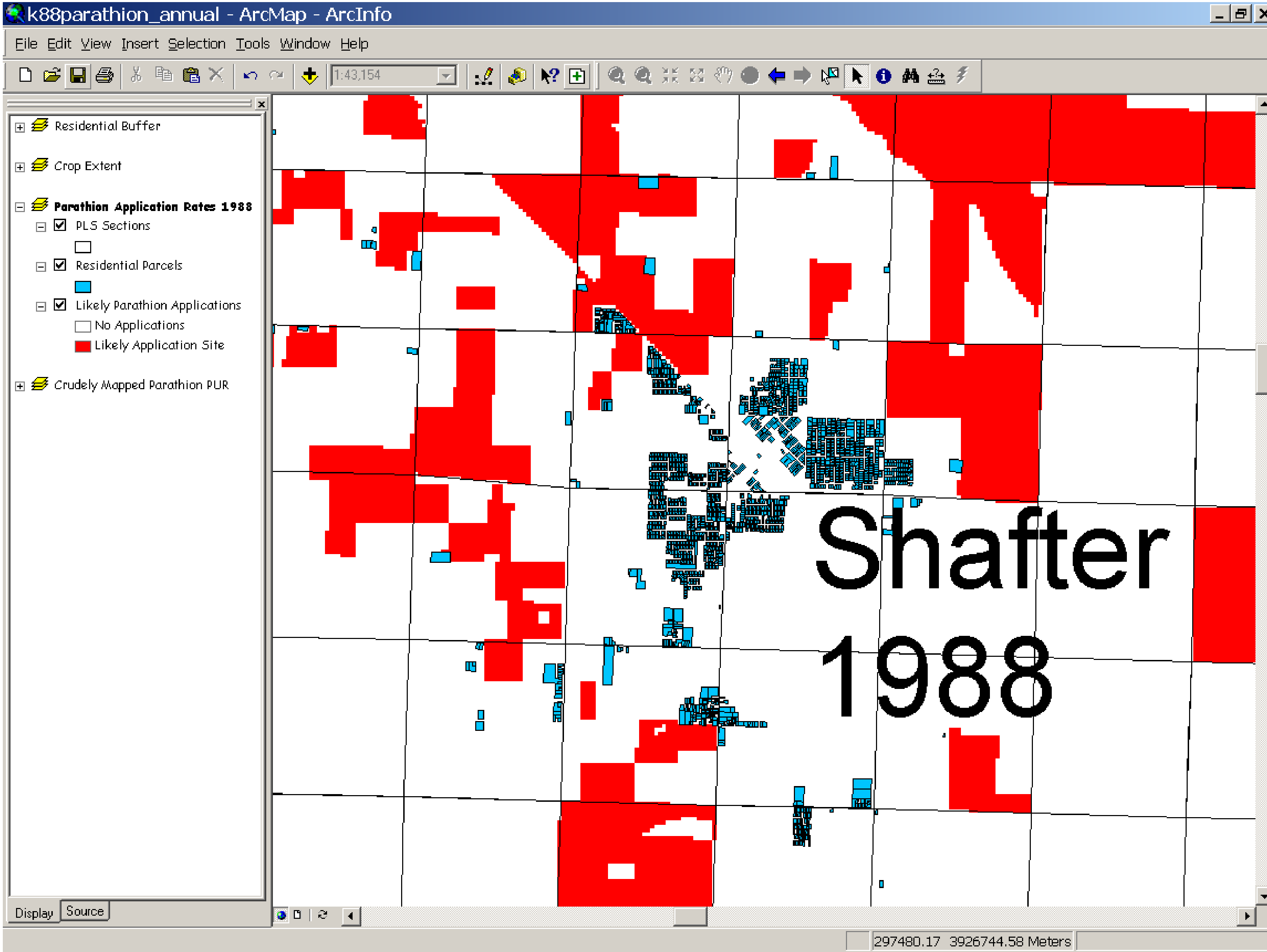
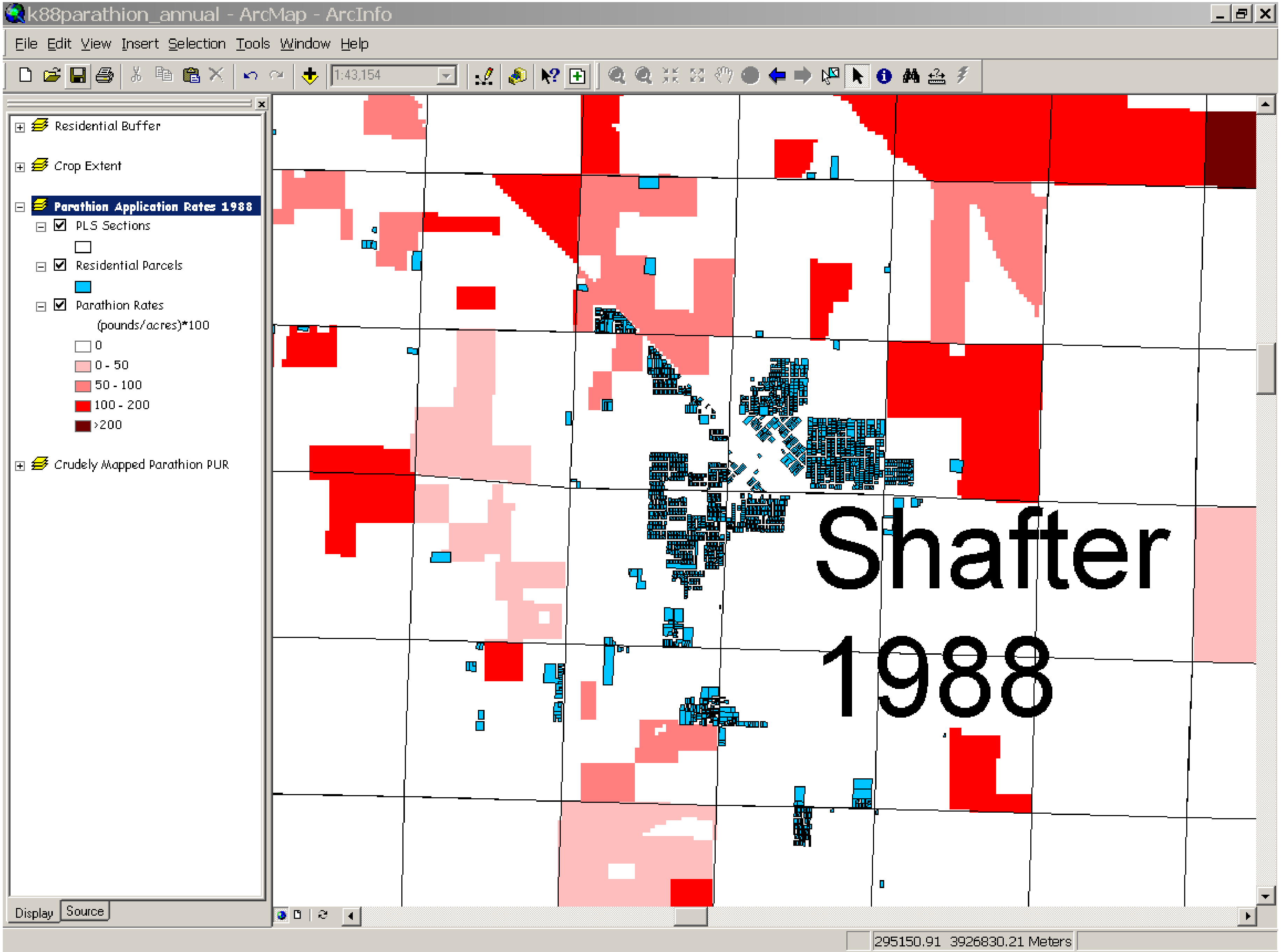
Example of an original paper land-use map

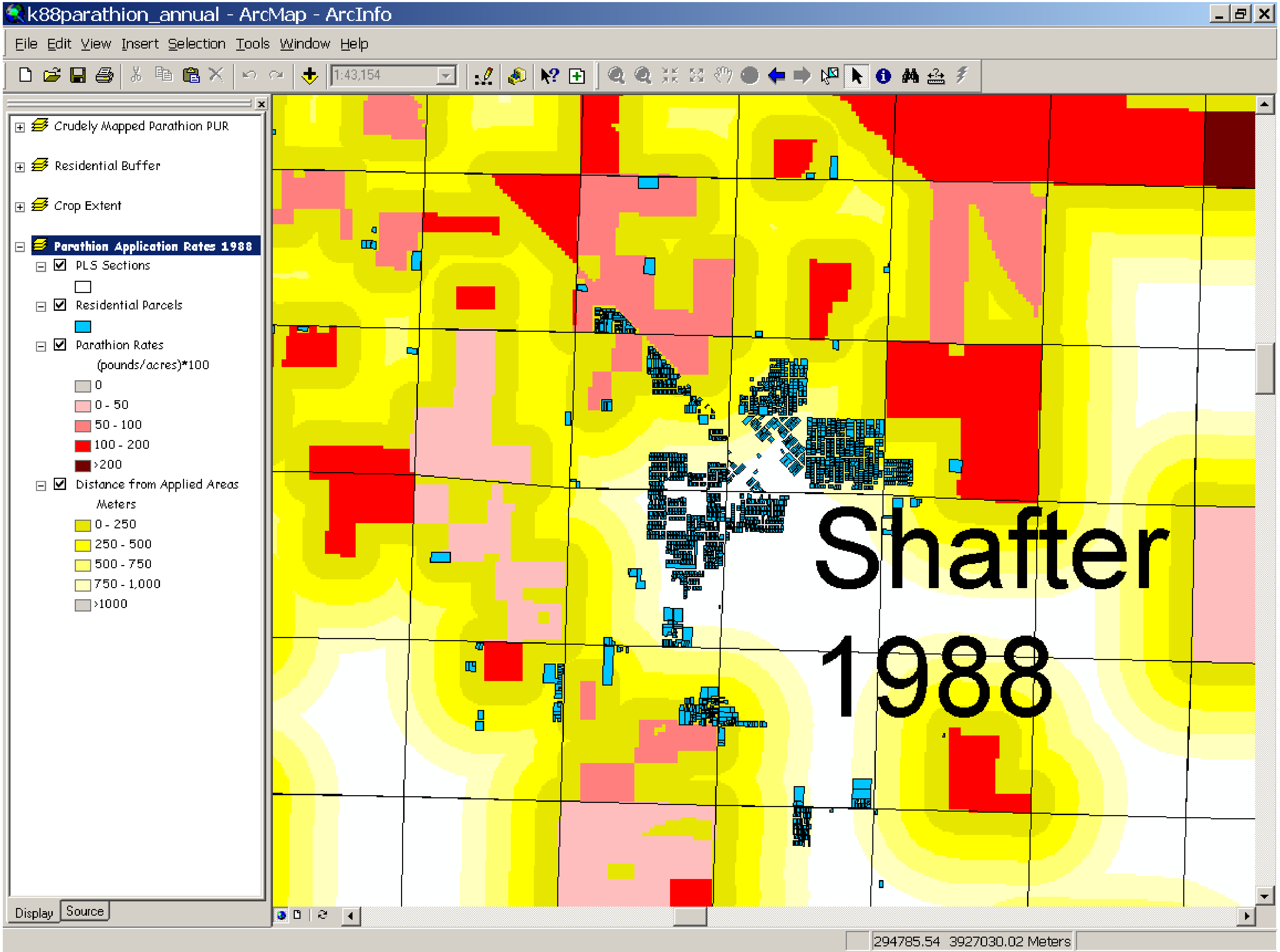
= 1 square-mile section

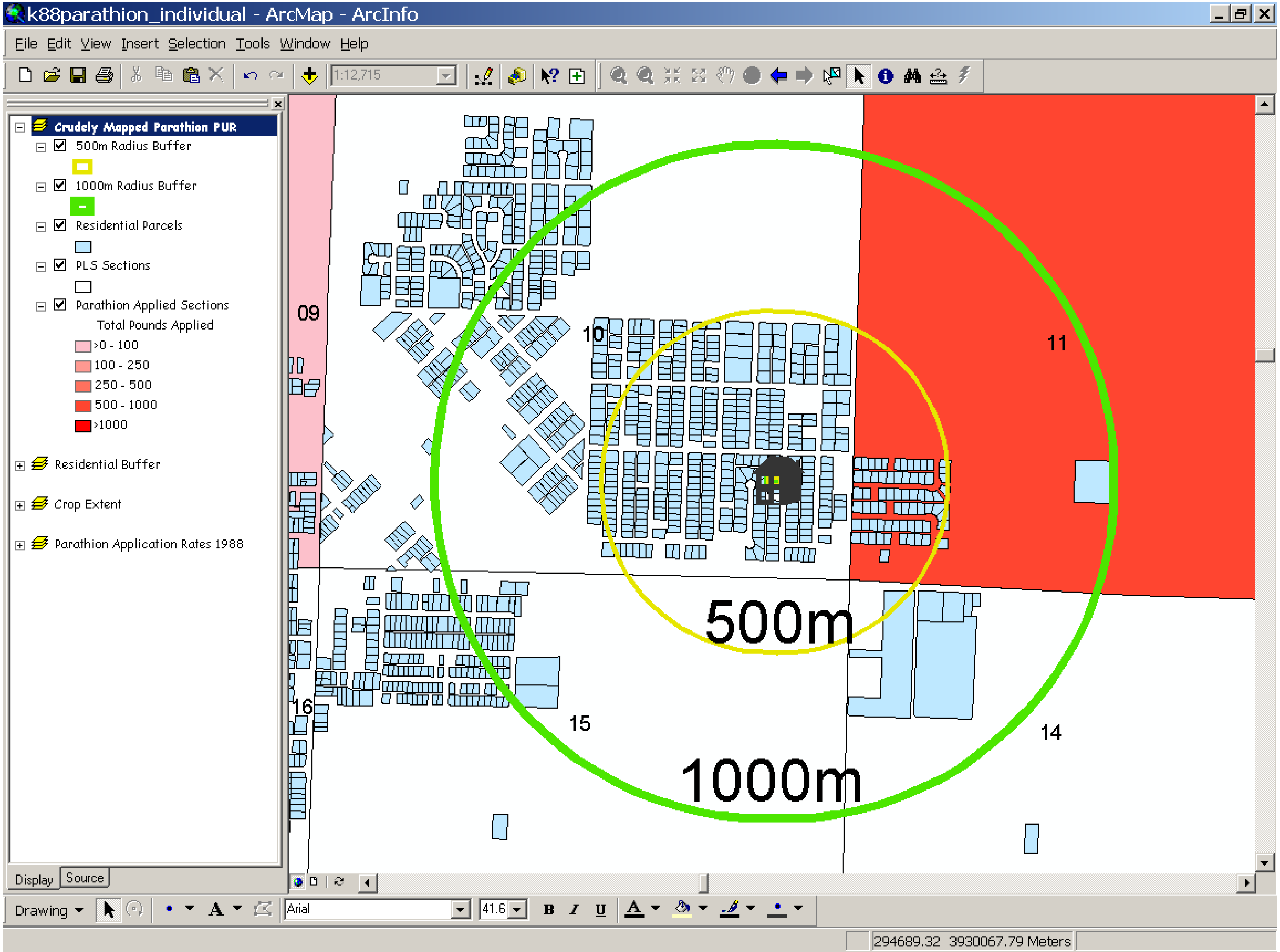



k88parathion_annual - ArcMap - ArcInfo
File Edit View Insert Selection Tools Window Help
1:43,253
Crudely Mapped Parathion PUR
Residential Buffer
Crop Extent
Shafter Agriculture 1990
Non-crop areas
Orchards and Crops
Almonds
Grapes
Apples
Kiwi
Pistachios
Peaches/nectarines
Plums
Field crops
Parathion Applied Sections
P
Residential Parcels
Parathion Application Rates 1988
Display
Source
Shafter
297717.38 3926701.02 Meters


k88parathion_annual - ArcMap - ArcInfo
File Edit View Insert Selection Tools Window Help
1:43,154
Residential Buffer
Crop Extent
Parathion Application Rates 1988
PLS Sections
Residential Parcels
Likely Parathion Applications
No Applications
Likely Application Site
Crudely Mapped Parathion PUR
Display
Source
Shafter
1988
297480.17 3926744.58 Meters


k88parathion_annual - ArcMap - ArcInfo
File Edit View Insert Selection Tools Window Help
1:43,154
Residential Buffer
Crop Extent
Parathion Application Rates 1988
PLS Sections
Residential Parcels
Parathion Rates
(pounds/acres)*100
0
0 - 50
50 - 100
100 - 200
>200
Crudely Mapped Parathion PUR
Display
Source
Shafter
1988
295150.91 3926830.21 Meters


k88parathion_annual - ArcMap - ArcInfo
File Edit View Insert Selection Tools Window Help
1:43,154
Crudely Mapped Parathion PUR
Residential Buffer
Crop Extent
Parathion Application Rates 1988
PLS Sections
Residential Parcels
Parathion Rates
(pounds/acres)*100
0
0 - 50
50 - 100
100 - 200
>200
Distance from Applied Areas
Meters
0 - 250
250 - 500
500 - 750
750 - 1,000
>1000
Display
Source
Shafter
1988
294785.54 3927030.02 Meters

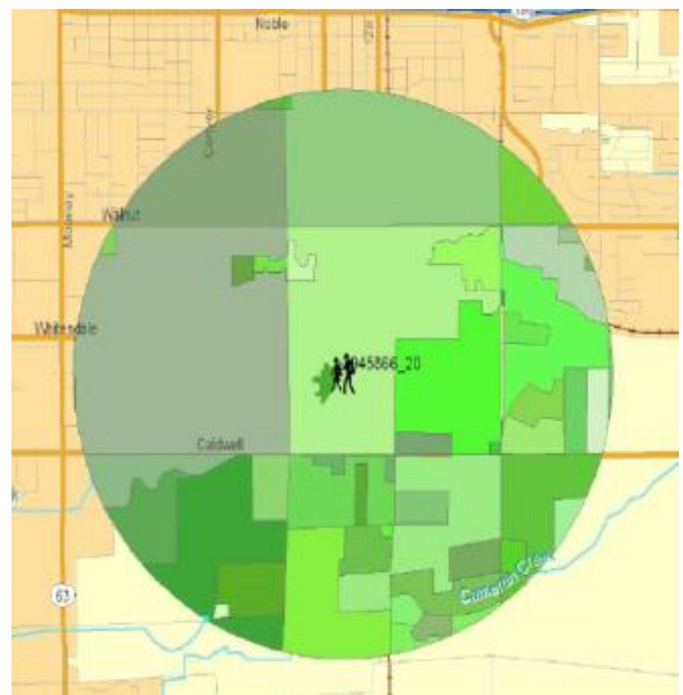

k88parathion_individual - ArcMap - ArcInfo
File Edit View Insert Selection Tools Window Help
1:12,715
Crudely Mapped Parathion PUR
500m Radius Buffer
1000m Radius Buffer
Residential Parcels
PLS Sections
Parathion Applied Sections
Total Pounds Applied
>0 - 100
100 - 250
250 - 500
500 - 1000
>1000
Residential Buffer
Crop Extent
Parathion Application Rates 1988
Display
Source
09
10
11
15
14
16
500m
1000m
Drawing
Arial
41.6
294689.32 3930067.79 Meters

Developed GIS system collabortions with Dr. Cockburn at USC-LA Cancer Registry:

Geographic **R**esidential **A**utomated **P**esticide **E**xposure **S**ystem **(GRAPES)**

GRAPES steps:

- **Geocode residences**
- **Draw 500 (or 1000) m buffer around a residence**
- **Calculate annual pesticide application per acre in each buffer based on PUR and land use (crops)**



Can we validate our PUR based exposure model?

DDT bio-concentrates in the food chain and fatty tissue of humans.

DDT/DDE exposure is ubiquitous and DDE can be found in everyone's serum in this room

- DDT, and DDE last in the soil for a very long time; potentially hundreds of years
- DDT/DDE may be deposited near application sites: Significant concentrations of DDT have been found in the atmosphere over agricultural plots
- People who work or live around contaminated sites might be exposed by having skin contact, inhaling DDT vapor, or breathing in DDT in dust.

Predicting Lipid-Adjusted Blood DDE levels (n = 46 Kern County PEG subjects)

	Correlation Coefficient	P-value	Estimate from linear regression	SE	P-value
PUR Organo-chlorine exposure measure	0.36	0.01	0.005	0.002	0.02
BMI	-0.17	0.26	-0.02	0.02	0.16
Age	0.32	0.03	0.03	0.01	0.004
Female	-	-	1.04	0.24	<.0001
Mixed and Loaded Pesticides by Hand	-	-	1.21	0.34	0.001
Used Pesticides in the Home	-	-	0.48	0.22	0.03
Model Adjusted R^2	-	-	0.46		



Conclusions

- Exposure misclassification is a major factor for not being able to identify associations with environmental factors

- Statistical limitations of rare disease investigations
  - Poor power for ranking exposures, testing interactions, or examining specific exposures

Emphasis on pooling data and resources

- biologic specimen and
- exposure assessment



Many Thanks To….

Rudy Rull, PhD

Northern California Cancer Center

Myles Cockburn

USC-Preventive Medicine and LA County Cancer Registry

Exposure Data

- California Dept. of Pesticide Regulation
- California Dept. of Water Resources