Will Rising Herbicide Use in the Midwest Raise Reproductive Risks?
The Herbicide Use and Birth Outcomes in the Midwest Project

www.cehn-healthykids.org

Session Outline

- **Introduction to the Herbicides in the Midwest Project**
  James Roberts, MD, MPH
- **Trends in Herbicide Use and Exposures**
  Charles Benbrook, PhD
- **Insights from Past Research**
  Melissa Perry, PhD
- **Emerging Science and Birth Center Challenges**
  Paul Winchester, MD
- **Open Discussion**
  Panel Members

Introduction to Herbicides and Birth Outcomes in the Midwest

James Roberts, MD, MPH
Project Goal

Assure that farmers and our food system do everything possible to support the health of children
• Conception—pregnancy—birth
• Early growth & development
• Adulthood

At it’s core, this project is about supporting healthy pregnancies and normal childhood development.

Project Activities

Conduct and publish research on trends herbicide use, toxicity, and health effects.

• Synthesize and disseminate published research
• Emphasize supporting positive patient outcomes, epidemiological advances
• Improve accuracy of herbicide use metrics around rural communities
• Enhance exposure estimates through:
  o GPS modeling
  o Biomonitoring data
  o Environmental sample results
More Project Activities

Assess options to reduce herbicide use, exposures, and risk
• Enhance birth and death certificates
• Improve integration of birth defects registries and medical records

Identify and promote prudent actions to mitigate known risk drivers
• Limit the applications of these known risk drivers
• Support herbicide resistant management plans to slow down the “herbicide treadmill”

Project Science Team

• Charles Benbrook, Benbrook Consulting Services
  o PhD in Agricultural Economics from University of Wisconsin-Madison
• Michael Hansen, Consumers Union
  o PhD in Ecology and Evolutionary Biology from University of Michigan
• Irva Hertz-Picciotto, University of California- Davis
  o PhD and MPH in Epidemiology and MA in Biostatistics, University of California- Berkley
• Richard Jackson, University of California- Los Angeles
  o MD from the University of California-San Francisco, and MPH in Epidemiology, University of California – Berkeley
Project Science Team, Continued

- Philip Landrigan, Mount Sinai School of Medicine
  - MD, Harvard University and MS in Occupational Medicine from the London School of Hygiene and Tropical Medicine
- Bruce Lanphear, Simon Frasier University, BC Children’s Hospital, and Cincinnati Children’s Hospital Medical Center
  - MD, University of Missouri- Kansas City, MPH from Tulane School of Public Health and Tropical Medicine
- Routt Reigart, Medical University of South Carolina
  - MD, Harvard Medical School
- Paul Winchester, Franciscan St. Francis Health and Riley Children’s Hospital
  - MD, University of Colorado Medical Center, MA University of Michigan

Why the Focus on Herbicide Use in the Midwest?
Four Concerns

1. Reproductive problems
   • Spontaneous abortions, failure to conceive

2. Adverse Birth Outcomes
   • Premature delivery, low-birth weight, birth defects

3. Developmental Effects
   • Neurological, immune system, metabolic

4. Epigenetic Effects
   • Metabolism, CVD, obesity, diabetes, neurobehavioral

The Challenge

Can we prevent an increase in the frequency/severity of herbicide-driven reproductive problems and adverse birth outcomes among women and children in heavily farmed regions of the Midwest?

Or, will we struggle to catch-up after such increases have already occurred?
Introducing a New CEHN Project: Herbicides and Birth Outcomes in the Midwest

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Trends in Herbicide Use and Exposures

Charles Benbrook, PhD
Major Drivers of Herbicide Risk... It’s Complicated!

- Herbicide use – how many, how often, when, and at what rates?
- Exposure routes, levels, and cumulative exposures
  - Food
  - Beverages and drinking water
  - Air and dust

And Also...

- A person’s health status and genetics
- The timing of exposures
- Herbicide metabolism and pharmacokinetics
- Exposed tissues, levels, and duration of exposures
- Toxicity of herbicide active ingredients and formulated products
Tracking the Intensity of Herbicide Use in Public Health Research

Pounds of herbicide active ingredient (a.i.) applied is only one of several essential indicators of herbicide use. Others include:

- How many different a.i.’s are sprayed annually
- Number of applications of each a.i. and all a.i.’s collectively
- Herbicide rates of application (pounds a.i./acre)

Additional Herbicide Metrics Important to Farmers

- The number/diversity of weed species controlled by each herbicide
- How long each application controls target weeds
- Whether any weeds are resistant to a given herbicide

These factors determine weed management system costs, efficacy, environmental impacts, and sustainability.
Why the Focus on Rising Herbicide Use in the Midwest?

• Glyphosate (Roundup) is by far the most heavily applied herbicide on soybeans and corn
• Fastest-growing region in terms of overall herbicide use and herbicide toxicity
  o Driven by spread of glyphosate-resistant weeds
  o Use peaked in the SE in 2015-2016

A picture tells a thousand words...

U.S Area Infested with Glyphosate Resistant Weeds (millions of acres)

Milestones in the Emergence and Spread of Glyphosate-Resistant Weeds

Example of Project Citation and Bibliography from Website

2B: Routes of Exposure

Herbicides are extensively used all around the country and often become airborne or run off into streams or rivers, acting in their spread beyond the farm fields. In one study, USGS scientists report glyphosate runoff increased 50-80% of air and rain samples examined Chang et al., 2013, demonstrating that routes of exposure extend beyond applicators with direct contact with herbicides.

Chang et al., 2011


ABSTRACT:

This is the first report on the ambient levels of glyphosate, the most widely used herbicide in the United States, and its major degradation product, aminomethylphosphonic acid (AMPA), in air and rain. Concurrent, weekly integrated
Bibliography Functionality

• Goal – Provide an on-ramp to extensive data and literature on herbicide use, exposures, risks, and weed management system choices.

Project Bibliography

Bibliographies Grouped by Term:
Adjuvants | Biomonitoring | Birth Defects | Cancer Risks | Crop Science | Developmental Impacts | Endocrine Disruptors | Epigenetic Impacts | Ethics and Environmental Justice | Female Reproductive Impacts | Male Reproductive Impacts | Other Health Risks | Oxidative Stress | Policy and Politics | Remediation | Routes of Exposure | Weed Management Systems

• Items include link to full text where available!

Targeted Searches

To find citations and information on “Birth Defects”, click on the item in the list of keyword tags, and then scan through the results:

Chevrier et al., 2011
Cecile Chevrier, Gwendolina Limos, Christine Monfort, Florence Rouget, Ronan Garlantezec, et al., “Urinary biomarkers of prenatal atrazine exposure and adverse birth outcomes in the PELAGIE birth cohort,” Environmental Health Perspectives, 2011, 119(7), DOI: 10.1289/ehp.100277. ABSTRACT: BACKGROUND: Despite evidence of atrazine toxicity in developing organisms from experimental studies, few studies—and fewer epidemiologic investigations—have examined the potential […]

Winchester et al., 2009
Weed Resistance -- Bad News for Farmers, the Environment, and Public Health

A few key milestones:

1996  Introduction of GE herbicide-resistant (GE-HR) crops, only one glyphosate-resistant weed on minor acreage in the Western US

2001  56 million acres of GE-HR corn and soybeans planted, first confirmed case of a glyphosate-resistant (GR) weed, marestail in Delaware after four years of RR crops

2007  107 million acres of GE-HR corn+beans planted, ~15 GR weeds, estimated 20 million acres of GR weeds (~19% of total GE-HR corn and soybeans)

2012  143 million acres of GE-HR corn+beans, ~22 GR weeds, 61 million acres of GR weeds (~43% of total GE-HR corn+bean acres)

2017  (projected) 162 million acres of GE-HR crops, ~32 GR weeds, ~130 million acres of GR weeds (~80% of GE-HR acres!)

Why Worry About the Future of Herbicide Use and Adverse Birth Outcomes in the Midwest?

Changes expected over the next 5 crop years (2017-2021):

- Nearly all corn/soybean acres will be infested with glyphosate-resistant (GR) weeds
- Steady increase in number of acres infested with 2, 3, or 4 GR weeds
- By 2020, the percent of acres with 3 or more GR weeds will likely exceed the percent of acres with 1 or none
- Growing percent of GR weeds resistant to multiple herbicides
  - Possible result >> no viable and affordable herbicide-based control options
More Why Worry?

Next steps by pesticide-biotech-seed industry:

- Double down on next-gen GE-HR crops immune to multiple herbicides
- Billions invested in 2,4-D and dicamba resistant crops, production plants, and distribution systems

- EPA approval for multiple new herbicides that allow post-emergence applications at higher rates and for longer periods (~4 months instead of only 1)

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**Projected Increase in 2,4-D Use on 2,4-D HR Corn Based on Projections by Dow AgroSciences of Acres Planted and Average Rates of Application per Crop Year (see notes)**

<table>
<thead>
<tr>
<th>Metric</th>
<th>2011</th>
<th>2015</th>
<th>2017</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corn Acres Planted (million)</td>
<td>91.9</td>
<td>88.0</td>
<td>90.0</td>
<td>88.5</td>
</tr>
<tr>
<td>% Acres Treated with 2,4-D on Acres Not Planted to 2,4-D HR Seeds</td>
<td>6.5%</td>
<td>11%</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>% Acres Planted to 2,4-D-Resistant Seeds</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acres Planted to 2,4-D-Resistant Seeds</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate of Application per Crop Year on Non-2,4-D HR Acres (pound a.i./acre)</td>
<td>0.5</td>
<td>0.61</td>
<td>0.61</td>
<td>0.61</td>
</tr>
<tr>
<td>Rate of Application on 2,4-D HR Acres (pound a.i./acre)</td>
<td></td>
<td></td>
<td>0.875</td>
<td>0.875</td>
</tr>
<tr>
<td>Number of Applications</td>
<td></td>
<td></td>
<td>1.33</td>
<td>1.33</td>
</tr>
<tr>
<td>Rate per Crop Year</td>
<td></td>
<td></td>
<td>1.16</td>
<td>1.16</td>
</tr>
<tr>
<td>2,4-D Applied, All Acres (million pounds a.i.)</td>
<td>2.99</td>
<td>5.90</td>
<td>20.65</td>
<td>50.13</td>
</tr>
</tbody>
</table>

**Notes:**
1. Corn acreage planted data and forecasts from USDA.
2. % acres treated and rates in 2011 and 2015 from USDA-NASS, Quickstats.
3. Acreage planted to 2,4-D HR corn and rates in 2017 and 2020 are based on Dow AgroSciences projections, as reported in Appendix 4. in the USDA-APHIS Environmental Impact Statement (USDA 2014).
4. The Enlist Duo label allows for a maximum rate per crop year of 2 pounds/acre.
### Projected Increase in 2,4-D Use on 2,4-D Resistant Soybeans Based on Projections by Dow AgroSciences of Acres Planted and Average Rates of Application (see notes)

<table>
<thead>
<tr>
<th>Metric</th>
<th>2011</th>
<th>2015</th>
<th>2017</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soybean Acres Planted (million)</td>
<td>77.4</td>
<td>82.7</td>
<td>85.5</td>
<td>84.5</td>
</tr>
<tr>
<td>% Acres Treated with 2,4-D on Acres Not Planted to 2,4-D HR Seeds</td>
<td>13.7%</td>
<td>17.2%</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>% Acres Planted to 2,4-D HR Seeds (millions)</td>
<td>15</td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined Acres Treated</td>
<td>10.6</td>
<td>14.2</td>
<td>23.6</td>
<td>44.8</td>
</tr>
<tr>
<td>Rate per Crop Year on Non-2,4-D HR Acres (pound a.i./acre)</td>
<td>0.51</td>
<td>0.53</td>
<td>0.53</td>
<td>0.53</td>
</tr>
<tr>
<td>Rate of Application 2,4-D HR Acres (pound a.i./acre)</td>
<td>0.875</td>
<td></td>
<td>0.875</td>
<td></td>
</tr>
<tr>
<td>Number of Applications</td>
<td>1.00</td>
<td>1.04</td>
<td>1.54</td>
<td>1.54</td>
</tr>
<tr>
<td>Rate per Crop Year 2,4-D HR Acres (pound a.i./acre)</td>
<td>1.35</td>
<td>1.35</td>
<td></td>
<td></td>
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<tr>
<td>2,4-D Applied, All Acres (million pounds a.i.)</td>
<td>5.41</td>
<td>7.54</td>
<td>24.74</td>
<td>54.82</td>
</tr>
</tbody>
</table>

Notes:
1. Soybean acreage planted data and forecasts from USDA.
2. % acres treated and rates in 2011 and 2015 from USDA-NASS, Quickstats.
3. Acreage planted to 2,4-D HR soybeans and rates in 2017 and 2020 are based on Dow AgroSciences projections, as reported in Appendix 4. in the USDA-APHIS Environmental Impact Statement (USDA 2014).
4. The Enlist Duo label allows for a maximum rate per crop year of 2.85 pounds/acre.

### Projected Increase in Dicamba Use on Xtend HR Soybeans Based on Monsanto’s Projection of Acres Planted and Average Rates of Application per Crop Year (see notes)

<table>
<thead>
<tr>
<th>Metric</th>
<th>2010</th>
<th>2015</th>
<th>2017</th>
<th>2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soybean Acres Planted (million)</td>
<td>77.4</td>
<td>82.7</td>
<td>85.5</td>
<td>84.5</td>
</tr>
<tr>
<td>% Acres Treated with Dicamba on Acres Not Planted to Dicamba HR Seeds</td>
<td>0.5%</td>
<td>0.8%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>% Acres Planted to Dicamba HR Seeds</td>
<td></td>
<td></td>
<td>65.1%</td>
<td></td>
</tr>
<tr>
<td>Xtend Planted Acres (million)</td>
<td>15</td>
<td>55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate per Crop Year Non-Dicamba HR Acres (pound a.i./acre)</td>
<td>0.19</td>
<td>0.275</td>
<td>0.275</td>
<td>0.275</td>
</tr>
<tr>
<td>Dicamba Rate per Crop Year on HR Acres (pound a.i./acre)</td>
<td>1.25</td>
<td>1.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dicamba Applied, All Acres (million pounds a.i.)</td>
<td>0.07</td>
<td>0.18</td>
<td>18.99</td>
<td>68.98</td>
</tr>
</tbody>
</table>

Notes:
1. Soybean acreage planted data and forecasts from USDA.
2. % acres treated and rates in 2011 and 2015 from USDA-NASS, Quickstats.
3. Acreage planted to dicamba HR soybeans and rates in 2017 and 2020 are based on Monsanto projections.
4. Both the BASF and Monsanto postemergence labels for dicamba on HR soybeans allow up to 2.0 pounds a.i. per crop year.
Insights from Past Research

Melissa Perry, PhD

Knowledge Base

- Nearly two dozen papers from rural birth center studies in the 1990s
- Several epidemiological studies on atrazine and 2,4-D
- Limited but growing biomonitoring data
- Results of multiple Agricultural Health Study projects

- Numerous published animal studies assessing impacts on reproduction and development
Biomonitoring Confirms Widespread Herbicide Exposures

Glyphosate and AMPA (primary glyphosate metabolite) residues in human urine have been rising in the U.S. population since around 2005, and have increased about a 4-fold in many people.

In 2009-2010, CDC sampled the urine of 2,747 people...

CDC Study Results

• Geometric mean of urinary 2,4-D levels was 0.308 µg/l (microgram per liter, or ppb) (CDC, 2015)
• U.C. San Francisco team found glyphosate residues in the urine of 93% of study participants
• Detailed results for glyphosate residues as reported by (Adams et al., 2016):

<table>
<thead>
<tr>
<th>Type</th>
<th>Number of Samples</th>
<th>Glyphosate Residue (µg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>75</td>
<td>2.9</td>
</tr>
<tr>
<td>Men</td>
<td>56</td>
<td>3.3</td>
</tr>
<tr>
<td>Children</td>
<td>7</td>
<td>3.6</td>
</tr>
</tbody>
</table>
Birth Center Study Results

Glyphosate, 2,4-D, and dicamba were among the herbicides identified as increasing the risk of adverse reproductive outcomes.

Key Insight

**Greatest risk** of herbicide-induced reproductive problems and birth defects occurs when the period from **one month prior to conception through the first trimester of pregnancy** coincides with the herbicide spraying season.

References:
(Albucke et al., 2001; Chevrier et al., 2011; Garry et al., 1996, 2002; Rappazzo et al., 2016; Schreinemachers, 2003, 2010; Winchester et al., 2016)
So, what is the spray season in the Midwest?

• Historically, heavy herbicide spray season lasted 6 weeks to 2 months
• New GE herbicide-resistant crops will extend the spray season to at least 4 months
• Mid to late summer applications will lead to new routes of exposure via food, drinking water, and the air

Key Study: Pesticide Applicators and Farm Families in the Minnesota’s Red River Valley
(Garry et al., 1996, and 2002)

• Highest odds ratio across all associations for glyphosate and neurobehavioral disorders (ADHD; OR=3.6)
• Glyphosate applied by one or both parents of 6 children with ADD/ADHD, out of a total 14
• Study took place before widespread planting of GE-HR crops
Other Key Insights from *Garry et al., 2002*

- Only 63% of birth defects diagnosed in first year of an infant’s life
- 26% diagnosed at age 3 or later
- Need to track children for several years to fully capture adverse birth outcomes

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Emerging Science and Birth Center Challenges

Paul Winchester, MD
Background

- 300 million pounds of glyphosate (GLY) (Roundup®) are applied each year in the US
- Though glyphosate has been in use since 1974, no previous measures of GLY exposure in US pregnancies have been published
- Rodent models of pesticide exposure in pregnancy correlate with adult and transgenerational disease through epigenetic mechanisms
- Measured GLY in pregnant women to estimate fetal exposure and potential adverse effects on pregnancy outcomes

Environmentally Induced Epigenetic Transgenerational Disease

How does it work?

- Chemicals (or stressors) in environment
- Induce DNA methylation of genome (in child, adolescent or fetus)
- Which alters adult disease risk (shifts in gene expression)
- And can be transmitted to future generations
Pregnant Rat
Vinclozolin Exposure (PC days 8-14)
Offspring

Failed Experiment!
The Baby Rats Were Normal

Adult Rats had Diseases
Fetal Exposure: Adult disease

- Low sperm count
- Infertility
- Cancer
- Kidney
- Prostate
- Pregnancy abnormalities
- Immune dysfunction
- High cholesterol
- Accelerated aging
- Non “Sexy” scent
- Anxiety prone

Transgenerational Effects of Fetal Pesticide Exposure
Declining Age of Menarche (Japan)

Males Developing 2 years Earlier Too!

BMC Women's Health 2012 Jul 16;12(1):19
Hosokawa, Imazeki, Mizunuma, Kubota, Hayashi
New Study: Objectives

Prospective cross-sectional birth cohort study to measure:

• How many Midwest pregnant women are exposed to glyphosate (GLY)?
• Is drinking water an important source of exposure?
• What risk factors and adverse pregnancy outcomes correlate with exposure?

Design/Methods

• Pregnant women ages 18-40 years, newborn infants enrolled prospectively at a private obstetrical practice
• Same day urine and household water samples were collected during a subsequent clinical visit
• Urine and water samples were measured for GLY in ng/mL with liquid chromatography-tandem mass spectrometry (LLOQ 0.5 ng/mL)
Design/Methods, continued

- Electronic medical records reviewed and pregnancy outcome data were collected
- Food and water consumption questionnaires administered during pregnancy
- Statistical linear models used to assess relationships between GLY level and clinical outcomes of gestation age and adjusted birth weight, as well as pregnancy-related risk factors

Study Population

- A total of 69 pregnant women with live-born infants were studied
- 69 drinking water samples were tested
- Mean maternal age was 29 years (range 18-39 years)
- Maternal race was 94.2% Caucasian, 7.8% Asian
Results

- 65 of 69 pregnant women (91%) tested positive for GLY (>LLOD)
- Mean GLY concentration was 3.6 ±0.12 ng/mL
- None of the drinking water samples had detectable GLY, suggesting that diet and beverages likely source of exposure
Maternal Weight vs. Glyphosate Levels

**Glyphosate vs. Maternal BMI (Prepregnancy)**

- Healthy weight
- Overweight
- Obese

- Glyphosate (ng/mL)
- Maternal BMI
- Prepregnancy Obesity (≥ 30 BMI) vs. GLY

- GLYPHOSATE (ng/mL)
- Maternal BMI
- Prepregnancy Obesity (≥ 30 BMI) vs. GLY

- R = 0.286
- p = 0.017

- Prepregnancy Obesity (≥ 30 BMI) vs. GLY

- Glyphosate vs Prepregnancy Obesity
- 18.9-29.3
- 30-39.5

- p = 0.0268
Caffeine vs. Glyphosate

Do you currently consume beverages containing caffeine (coffee, caffeinated soda, tea, energy drinks)?

Pregnancy Length vs. Glyphosate

* Only includes singleton ≥37 week gestation infants.
Gestation-Corrected Birth Weight (Bwt %tile) vs. Glyphosate

Summary

• The most heavily used pesticide in the US is found in over 90% of pregnancies in a Midwestern state
• Higher GLY levels were associated with shorter gestations and with lower gestation-adjusted birth weights
• Since water samples were largely negative, the source of exposure is probably food
• Maternal pre-pregnancy weight and caffeine intake were associated with higher GLY
Study Implications

• The majority of fetuses must be assumed to have exposure to glyphosate during critical periods of fetal development

• Policy makers need to ensure that significant increases in herbicide use and fetal exposures in the Midwest do not result in altered DNA methylation and potential multigenerational disease

Limitations

• Small sample size and regional and demographic differences are not addressed – but study is ongoing, with many more samples by the end of 2017

• No $$ to exam GLY variability by trimester and comparisons in blood

• GLY residues in food not addressed
Acknowledgements

Franciscan St. Francis Health Fairbanks Public Health
- Laboratory Technicians
- OB/GYN Physicians
- Labor & Delivery Nurses
- Post Partum Nurses
- Neonatal Intensive Care Nurses
  Medicine

OB GYN of Indiana South
Office Manager
- Medical Assistants
- Physicians
- Study Population

UCSF Department of Laboratory Medicine
- Grant Support
- Study Design Collaboration
- Co-PI

Indiana University
Neonatology Department
- Clinical Research Coordinator

Panel Discussion

Thank you!
Access this presentation under “Resources” and other information on the project website:
www.cehn-healthykids.org