Glyphosate Stewardship, Epidemiology, and the Farm Family Exposure Study

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Introduction

Glyphosate has very favorable toxicologic properties. It is not carcinogenic, mutagenic or neurotoxic and it is not a reproductive or developmental toxin *(1-3)*. Consumers have confidence in glyphosate formulations based on their efficacy and history of safe use. Other herbicidal active ingredients, like 2,4-D, have favorable toxicology profiles, but have negative public perceptions. We have been working to maintain glyphosate's favorable reputation through a strategy that anticipates challenges and puts appropriate initiatives in place. One of those initiatives is a unique research program called the Farm Family Exposure Study (FFES). Key FFES findings will be discussed as part of our overall glyphosate strategy.

Macro issues

The general public is selectively risk averse, especially about (perceived) risks to children's health. Individuals will assume known risks (e.g. cigarettes), yet object to infinitesimal (potential) risks from pesticide residues on foods or foreign DNA/protein in genetically modified (GM) crops. Anti-pesticide activists orient their allegations accordingly. Glyphosate is a prime target of anti-pesticide and anti-GM activists due to its widespread use and key role with glyphosate tolerant crops.

Allegations based on results from epidemiologic studies have begun to affect our freedom to operate.[a] In Canada, enabled by a recent Supreme Court ruling, localities have cited epidemiologic findings to ban "non-essential use" of pesticides, usurping federal regulations based on comprehensive risk assessments. There are now six published studies that arguably associate glyphosate and other pesticides with lymphopoietic cancers *(4-6)* or adverse reproductive outcomes *(7-9)*. Independent reviewers judge these studies to be poor quality. Nonetheless, these studies have caused controversy for glyphosate and for Roundup Ready regulatory submissions in Brazil and other world areas.[b]

Epidemiologic research on pesticides is a burgeoning field for academic and government researchers. The most prominent ongoing study is the U.S. government's Agricultural Health Study (AHS). The AHS involves numerous PhD level scientists from the National Cancer Institute, the National Institute for Environmental Health Sciences, and the Environmental Protection Agency and external expenditures approaching $50 million. This

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[a] Epidemiologists study people to identify factors that may cause or prevent disease. Agricultural researchers often have to rely on sketchy information about exposure and potential confounding factors.
[b] A Google internet search found 1,410 web pages touting a 1999 study that arguably linked glyphosate and non-Hodgkin's lymphoma.

study includes 75% of licensed pesticide applicators and their families in North Carolina and Iowa. The purpose of the AHS is to look for associations between farmers' reported use of pesticides and adverse health outcomes for them and their families (e.g. cancer, birth defects, child development, etc.). Numerous other studies are ongoing in the U.S., Canada, and Europe. Experience has shown that these studies will associate widely used pesticides with a number of diseases. The stage is set, therefore, for more allegations about human effects associated with glyphosate and other pesticides.

Strategy

Glyphosate stewardship consists of four elements: 1) publish relevant toxicologic, ecologic, and epidemiologic information about glyphosate in the peer reviewed literature *(3, 10-13)*; 2) review the literature regularly for glyphosate findings and respond when appropriate *(e.g. 14)*; 3) establish a network of prestigious scientists in key world areas and provide them the latest information about glyphosate; and 4) assess data gaps and fund appropriate research.

Data Gaps

The FFES was developed to fill two data gaps. First, there is a lack of information about applicator pesticide exposure under "real world" conditions. Epidemiologic studies assume that reported use of a pesticide is equivalent to a potentially hazardous exposure(s). Second, there is little empirical exposure information for farm children although children's health is a driving force in environmental regulation and a focus of epidemiologic research. Gladden et al. drew attention to farm spouses and children in a 1998 article *(15)*:

> *"Farming is unlike most other occupations in that the workplace is often the same as the worker's home. Thus families of farmers have unusual opportunities for indirect exposure to occupational hazards"*

The Natural Resources Defense Council made alarming allegations about risks to farm children in a report later that year *(16)*:

> *"There is an increasingly compelling body of scientific evidence indicating that farm children face particularly significant health risks." … Farm children are like canaries in the coal mine. … the record shows that U.S. EPA has failed to adequately consider the extensive evidence that children are exposed to significant amounts of pesticides …"*

By the time these reports appeared, we had organized an industry task force to assess the feasibility of the FFES. The task force approach enabled us to leverage costs[c] and technical expertise across a number of companies. In 1999, we completed a one-year pilot study that demonstrated feasibility and the FFES was initiated in 2000.

The purpose of the FFES is to characterize pesticide exposures for farm families by urinary biomonitoring before, during, and after a pesticide application. The study was coordinated by researchers at the University of Minnesota (UM), approved by the UM Institutional Review Board, and benefited from the advice of a distinguished panel of academic and government experts. FFES participants were randomly selected from licensed pesticide applicators in Minnesota and South Carolina. Families were eligible if there was a farmer, spouse, and at least one child between the ages of 4 and 17 living on the farm, if they owned or leased at least 10 acres of cropland, if they planned to apply at least one of the target pesticides (2,4-D, glyphosate, or chlorpyrifos) within one mile of their residence, if they were willing to collect all their urine for five consecutive days (the day before, the day of, and the three days after a pesticide application), and if they were willing to fill out pre-application and post-application questionnaires.

One hundred and six farm families participated in the study. Field staff observed pesticide applications and documented information relevant for exposure assessment. Recruitment began in 2000 and all fieldwork was completed by July 2001.

FFES Glyphosate Results

Forty-two participating farmers applied glyphosate in 2000.[d] Less than half (45%) of these farmers had detectable urinary glyphosate (> 1 part per billion (ppb) in urine) on the day of application, declining to 24% three days later. Urinary values were concentrated below or near the limit of detection (Figure 1) and the geometric mean on the day of application was 2 ppb. The highest observed value was 182 ppb - a level, if experienced daily for a lifetime, that would be 100 to 1000-fold below the U.S. reference dose[e] of 2 mg/kg/day.

Two of 42 farm spouses (5%) showed detectable values on the day of application - both at the limit of detection (Figure 2). There were no detectable values thereafter. Of 69 participating children, 5 (7%) had detectable values on the day of application, which declined to 3% three days after application. The highest

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[c] The FFES cost $2 million. Monsanto's share was $275,000. $150,000 was returned to Monsanto as reimbursement for glyphosate analyses.

[d] Five FFES farmers applied glyphosate in 2001. Results for these families are pending.

[e] The RfD is the regulatory value for daily absorbed dose that over a lifetime would not harm human health.

value for children was 20 ppb. All of the children with detectable values were involved in the pesticide mixing and application or were present in the pesticide mixing area.

Preliminary results for the other FFES chemicals (2,4-D and chlorpyrifos) show many more detectable values for all family members than were seen for glyphosate. For farmers, geometric mean values were much higher for the other chemicals than for glyphosate, though values for all chemicals were well within regulatory standards. Geometric mean values for spouses and children were slightly higher for the other FFES chemicals, though the differences were trivial. Data on 2,4-D and chlorpyrifos are still being processed and will be presented later this year at scientific meetings. Nonetheless, it is clear that glyphosate has a favorable exposure profile compared to these other FFES chemicals.

Implications

Results from the FFES show that self-reported use of glyphosate is not a reliable predictor of absorbed dose for applicators and that worst-case exposures are orders of magnitude below regulatory limits. Detectable urinary levels were found to be rare for spouses and children. Detectable levels for children were associated with helping or being present during pesticide mixing or application.

The FFES has become a key element in our scientific network briefings and in our responses to allegations about glyphosate. We're working actively to disseminate the results for glyphosate. FFES presentations have already occurred at 7 public meetings - including the last 3 AHS advisory panel meetings - and 10 peer-reviewed publications are planned. Longer term, we expect publication and presentation of these results to influence agricultural epidemiology positively. We are coordinating an international symposium later this year in Oxford, UK - convened by Sir Richard Doll - on pesticides and cancer. This affords an international scientific platform for the FFES data and for glyphosate toxicology data. The proceedings of this symposium will be published in the Scandinavian Journal of Work, Environment, and Health as a special supplement, making the FFES findings broadly available in a high profile publication.

The FFES provides "real world" information about how our pesticides are being used in the U.S. Subsequent analyses are planned to support predictive exposure models. Inspection of the FFES field reports for glyphosate show that children's exposure in the study, though trivial, probably could have been prevented by rudimentary precautions (e.g. wearing gloves when helping their fathers, taking care to avoid incidental contact with containers). Likewise, farmers' failure to wear gloves while mixing and loading was a common finding for those who showed detectable glyphosate values. We are currently looking to leverage the FFES data into a stewardship opportunity, perhaps in collaboration with EPA and agricultural organizations.

The FFES data are also being analyzed to assist with European re-registration. EU regulations call for thorough evaluation of operator exposure, usually based on very conservative predictive models. Some potential uses may be restricted unless relevant data can be presented. The FFES data provides a basis to challenge conservative predictions and may be useful to the workgroups that are currently developing/modifying the new (uniform) European predictive model (EUROPOEM).

Challenges

Monsanto's analytic chemistry expertise was essential to the FFES. However, our current method is outdated. It requires relatively large volumes of urine (100 ml, versus 5 ml for the 2,4-D and chlorpyrifos methods) and produces less precise results than methods for other FFES chemicals. Given the likelihood that human health allegations will continue to surface for glyphosate, it seems advisable to invest in modernizing the analytic method to increase analytic flexibility and precision.

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Appendix - Abbreviations

2,4-D - 2,4-dichlorophenoxy acetic acid

AHS - Agricultural Health Study

FFES - Farm Family Exposure Study

GM - genetically modified

ppb - parts per billion

RfD - Reference dose

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