MONSANTO

Backgrounder
Glyphosate and Reproductive Outcomes
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Glyphosate is one of many pesticides mentioned in three epidemiological reports that examine possible links between on-farm pesticide use and reproductive outcomes. All three reports--Savitz *et al.* (1997), Curtis *et al.* (1999), and Arbuckle *et al.* (2001) – use data from the Ontario Farm Family Health Study (OFFHS) (Arbuckle 1994). Savitz *et al.* (1997) investigated associations between reported pesticide use by males and pregnancy outcomes, specifically: miscarriage, pre-term delivery and small-for-gestational-age birth. Curtis *et al.* (1999) studied whether reported pesticide use by males or females was associated with delayed pregnancy, while Arbuckle *et al.* (2001) looked for associations between reported pesticide use and spontaneous abortion.

The OFFHS was a questionnaire-type study in which farm couples were asked to recall on-farm activities and pesticide usage on the farm during the previous 5 years. They were also asked to recall all pregnancy outcomes, 38% of which occurred more than 10 years before the survey. The farm couples lived year-round on a farm and the OFFHS investigators employed mail questionnaires to collect information about pregnancy outcomes from the mothers. Telephone follow-up was employed for non-respondents.

In the study by Savitz *et al.,* a number of specific pesticides had weak statistical associations with miscarriages and pre-term deliveries, but pesticides tended not to be associated with small for gestational age births. There were no statistically significant findings for glyphosate. In the study by Curtis *et al.,* for farms on which glyphosate was used, there was no significant association for women being engaged in pesticide activities. For men, glyphosate use was associated with a slight, but statistically significant, decrease in time to pregnancy. The authors dismissed this finding, which was contrary to their hypothesis that pesticide exposure delayed pregnancy, as probably due to uncontrolled factors or chance. Arbuckle *et al.* (2001) found that reported pre-conception use of phenoxyacetic acids, triazines, glyphosate, and thiocarbamates were weakly, but statistically significantly, associated with spontaneous abortions. Reported post-conception use was not associated with increased risk. The authors characterized the associations between pesticides and spontaneous abortions as "hypothesis generating" pending confirmation from other epidemiologic studies.

These studies are not convincing evidence of a relationship between glyphosate exposure and adverse pregnancy outcomes for a number of reasons:

1. **Uncertainty about exposure**

   There was no actual exposure data *per se* in these three epidemiologic studies. Exposures were assumed based on questionnaire responses by study subjects about farm activities and pesticide use. This type of information can be inaccurate. For example, according to a study by the National Cancer Institute, self-reports of pesticide usage were found to be only 60 percent accurate when compared with purchasing records (Blair & Zahm 1993). Further increasing the potential for inaccuracy is the fact that study subjects were only asked about pesticide use for the 5 years before the OFFS survey. These responses were assumed to be applicable to the entire farming careers of study subjects, an assumption inconsistent with changes in agricultural practice. Lastly, basing exposure estimation on questionnaire responses has the potential to be influenced by what epidemiologists call “recall bias.” This refers to the likelihood that families that experienced an adverse reproductive outcome are

more likely to remember use of certain pesticides than families that had only normal births. The most widely used pesticides, like atrazine, glyphosate, and 2,4-D, are most easily recalled and most likely to be over-reported.

2. **Low biological plausibility**

   Biologic plausibility is an important criterion for deciding whether a reported statistical association between a pesticide and a disease is likely to be valid. Glyphosate, even at very high doses in chronic feeding studies, does not cause adverse reproductive outcomes in laboratory animals (U.S. EPA 1993, EC 2002, WHO 2004, Williams *et al*, 2012). This makes statistical associations from epidemiologic studies less plausible.

3. **Inaccuracy of reported pregnancy outcomes**

   The OFFHS study relied exclusively on maternal self-reports of adverse pregnancy outcomes with no medical or other validation. Generally, scientists place less confidence in reports of health outcomes that are not validated with medical records.

4. **Confounding factors**

   A confounding factor is a cause of a disease that is correlated with another exposure being studied. Failure to control confounding factors, especially those that are strong causes of a disease, can create spurious associations between benign exposures and diseases. In the Arbuckle *et al.* study, there were at least three important potential confounding factors that were not controlled: history of previous spontaneous abortion, maternal age, and smoking. Even a weak correlation between these factors and use (or recall of use) of pesticides would produce spurious associations. In addition, in all three studies, the authors did not control the putative effect of one pesticide for the putative effects of other pesticides. So, for example, since farmers tend to use 4 or more pesticides each year, a disease that is associated with one pesticide will likely be associated with all, since their use patterns are correlated. In the absence of an analysis that controls for multiple pesticides, the best that can be said is that the findings for any individual pesticide might be due to its correlation with another pesticide.

In summary, three publications based on data collected in the OFFHS found associations between several pesticides and various adverse reproductive outcomes. There was no actual exposure data per se in these three epidemiologic studies. Exposures were assumed based on questionnaire responses by study subjects about farm activities and pesticide use. This type of information can be inaccurate. Glyphosate was not significantly associated with adverse reproductive outcomes in two of these studies (Savitz *et al.*, 1997; Curtis *et al.*, 1999). Glyphosate and other pesticides were weakly associated with spontaneous abortion in the study by Arbuckle (2001). However, the author did not control for important personal confounding factors or for multiple exposures and no actual exposure data was used, casting doubt on the validity of the findings in this study.

Biomonitoring data for glyphosate, collected as part of the Farm Family Exposure Study (FFES), provide assurance that human health effects related to glyphosate exposure are very unlikely. In the FFES, researchers from the University of Minnesota collected 5 days of urine samples from 48 farm families before, during, and after a glyphosate application (Mandel *et al.,*2005). Only 60% of farmers showed detectable exposure to glyphosate, with a 1 part per billion[1] limit of detection, and the maximum estimated absorbed dose was 0.004 mg/kg (Acquavella *et al.*, 2004). For farmers who apply glyphosate 10 times per year for 40 years, this maximum dose is

[1] 1 part per billion would be analogous to one pinch of salt in 10 tons of potato chips. http://www.nesc.wvu.edu/ndwc/articles/ot/fa04/q&a.pdf

approximately 30,000-fold less than the EPA reference dose[2] of 1.75 mg/kg/day. For spouses, only 4% showed detectable exposures and the maximum systemic dose was 0.00004 mg/kg/day.

Since glyphosate is not a reproductive toxicant in high-dose animal studies (U.S. EPA 1993, EC 2002, JMPR/WHO 2004, Williams *et al*, 2012), no evidence of a causal relationship between glyphosate exposures and adverse reproductive outcomes or malformations was identified in a review of epidemiologic literature of non-cancer endpoints (Mink *et al*., 2011). and since actual exposures on farms are so low (Acquavella *et al*, 2004), it is very unlikely that glyphosate would cause adverse reproductive outcomes for farmers or their spouses.

References

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[2] The reference dose is a "numerical estimate of a daily oral exposure to the human population, including sensitive subgroups such as children, that is not likely to cause harmful effects during a lifetime."." http://www.epa.gov/OCEPAterms/rterms.html (accessed November 13, 2014).

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