Message

From: GOLDSTEIN, DANIEL A [AG/1000] [/O=MONSANTO/OU=NA-1000-01/CN=RECIPIENTS/CN=527246]
Sent: 5/22/2008 1:54:12 AM
To: FARMER, DONNA R [AG/1000] [/O=MONSANTO/OU=NA-1000-01/CN=RECIPIENTS/CN=180070]
Subject: RE: Mandel draft

I'll have a look tonight before I head off... dag

-----Original Message-----
From: FARMER, DONNA R [AG/1000]
Sent: Wednesday, May 21, 2008 3:26 PM
To: GOLDSTEIN, DANIEL A [AG/1000]
Subject: RE: Mandel draft

Did you have a chance to review the draft? I would like to send this back to him by the end of this week. If you don't have time to review that is okay and I will send as is.

Thanks,

Donna

-----Original Message-----
From: CARR, KATHERINE H [AG/1000]
Sent: Wednesday, May 14, 2008 12:07 PM
To: FARMER, DONNA R [AG/1000]
Subject: RE: Mandel draft

See attached. << File: Glyphosate_Draft_RV032008drf_kc.doc >>

-----Original Message-----
From: FARMER, DONNA R [AG/1000]
Sent: Tuesday, May 13, 2008 4:50 PM
To: GOLDSTEIN, DANIEL A [AG/1000]; CARR, KATHERINE H [AG/1000]
Subject: Mandel draft

<< File: Glyphosate_Draft_RV032008drf.doc >>

I have put in some suggested edits to the Mandel/Mink glyphosate epi critical review study - mostly in the intro section. If you have the time I would appreciate your review.

Donna

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

TRIAL EXHIBIT 468

Case No. 3:16-cv-0525-VC

Date Entered _____

By _____
Deputy Clerk

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Introduction

Glyphosate (~~,~~ N-phosphonomethyl glycine)~~,~~ is the primary active ingredient in Roundup branded ~~, a popular~~ herbicides produced by the Monsanto Company. The United States (US) ~~-~~Enviromental Protection Agency (EPA) and other regulatory agencies around the world hasve registered this chemical as a broad-spectrum herbicide for use on multiple food and non-food use crops. ~~,~~ Glyphosate-based herbicides have been sold in the US since 1974 and are now registered in over 130 countries to control annual and perennial weeds, woody brush and trees in agricultural, industrial, forestry, greenhouse, rights-of-way and residential areas.

~~and for use at lower application rates as a plant growth regulator (US EPA 1993).~~ Generally, glyphosate-based products are water-based formulations containing ~~ted with~~ a salt form of the chemical (~~,~~ isopropylamine salt, sodium salt, potassuium salt or monoammonium salt)~~,~~ along with ~~water and~~ a surfactant ~~or water~~ to assist with penetrability of glyphosate into the target plant (Franz, 1997)~~, the solution~~. Glyphosate-based ~~,~~

~~Glyphosate-containing herbicides have been sold in the US since 1974 and are now registered in over 100 countries to control annual and perennial weeds, woody brush and trees, and regulate the growth of plants in agricultural, industrial, forestry, greenhouse, rights-of-way and residential areas (Williams et al. 2000). Pproducts containing glyphosate~~ have been marketed in the US under the brand names Roundup, Roundup Pro,

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and RodeoAquaMaster, Ranger, and many others internationally (WHO 1994NEED TO FIND a REF). [the preceding sentence might be better placed at the end of the first paragraph] In the US, In 2005, glyphosate (isopropylamine salt) herbicides wereas used applied toon 31% of all planted corn acres in 2005(USDA 2006) and 8892% of all planted soybeans acres in the US in 2006 (USDA 20062007).

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In plants, glyphosate inhibits the enzyme EPSPS (5-enolpyruvylshikimate-3-phosphate synthase), preventing plants from manufacturing sufficient quantities of three essential aromatic amino acids necessary to maintain growth. This aromatic amino acid biosynthetic pathway (the shikimic acid pathway) is unique to plants, some fungi and some bacteria, but is not present in insects, birds, fish, mammals and humansman (Franz et al., 1997). Animals and humans obtain these amino acids through their diet and do not use this enzymepathway. Thus, glyphosate has specific, selective toxicity to species that contain the shikimate acid pathway. This contributes to the and there is low risk to human health from the use of glyphosate according to label directions. Glyphosate acts by inhibiting the formation of aromatic amino acids at a step in this process that is unique to plants, therefore not presenting a risk to humans (Williams et al. 2000). This interrupts the production of an enzyme that is part of the shikimate pathway, enolpruvylshikimate phosphate synthase (EPSPS), which is necessary for the synthesis of chlorismate. This alteration in the pathway ceases the formation of three essential amino acids: phenyalanine, tyrosine, and tryptophan (Williams et al. 2000). [not sure Williams is the best reference here – there is no reference to the label in the article.]

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Gyphosate herbicides are only effective when applied directly to ~~the~~plant foliage. Upon application ~~of~~, glyphosate is translocated throughout the plant ~~, both roots and foliage of the treated plants are systemically eradicated (~~ (Franz, et al. 1997~~Malik et al. 1989~~).

Glyphosate binds very tightly to most soils and sediments in the environment and is essentially unavailable to plants after contact with soil. This explains why glyphosate-treated areas can be planted with crops soon after application. Research shows that glyphosate in soil is degraded over time by soil microorganisms (bacteria and fungi)~~Once glyphosate reaches the soil, microorganisms break it down~~ through various pathways into molecules such as carbon dioxide and inorganic phosph~~ate~~onic acid (~~Williams et al~~Gleisy et al. 2000).

Glyphosate is widely considered by regulatory authorities and scientific bodies to have no carcinogenic potential (US EPA 1993; EU, 2002; WHO/FAO 2004). In fact, the US EPA has classified glyphosate as Group E carcinogen, meaning that there is "evidence of non-carcinogenicity for humans" (US EPA, 1993). ~~Both the US EPA and the WHO have classified glyphosate as a noncarcinogenic and non-mutagenic chemical (US EPA 1997; WHO 1994).~~ Negative result were observed in Ggenotoxicity studies conducted under GLP (good laboratory practice) conditions and compliant with current regulatory test guidelines ~~revealed no activity and concluded that glyphosate does~~. It was concluded that ~~in the absence of carcinogenic potential in animals and the lack of genotoxicity in standard tests~~ glyphosate is unlikely to pose a carcinogenic risk to humans (~~not pose a risk to humans (~~Williams et al. 2000; WHO/FAO, 2004). In addition, in results from multigeneration reproduction studies and developmental toxicity studies in rats, no ~~did not~~

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~~indicate any~~ adverse effects were observed on the animals' ability to mate, conceive, carry or deliver normal offspring. The US EPA concludeds that there is a reasonable certainty that no harm will result to the general population and to infants and children from aggregate exposure glyphosate residues (US EPA, 2007).

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We reviewed epidemiologic studies of glyphosate and adverse health outcomes to evaluate the question of whether exposure to glyphosate is associated causally with cancer or non-cancer health risks in humans. In addition, we reviewed biomonitoring studies of glyphosate to allow for a more comprehensive discussion of issues related to exposure assessment (including exposure misclassification and information bias) and potential biological mechanisms as they relate to findings from the epidemiologic studies.

Methods

Multiple search strategies were employed to identify literature related to glyphosate exposure and human health outcomes. A PubMed search was conducted using the term "glyphosate," as well as its synonyms, chemical name, and CAS (Chemical Abstract Service) number, in conjunction with various terms related to epidemiology studies (e.g., "cohort," "case-control"). In addition, broader searches for articles regarding epidemiology studies of organophosphorus compounds used as pesticides or herbicides were conducted, as well as a search for case-control studies of pesticides or herbicides.

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A separate search was conducted using the STN search service index, which searches multiple databases simultaneously, including Biosis, EMBASE, Medline, Pascal, and SciSearch. The CAS registry number for glyphosate, 1071-83-6, was searched in combination with epidemiologic terms.

After duplicates were removed, abstracts were reviewed to determine if they met the inclusion criteria and for those that did the articles were obtained and reviewed.

Literature searches to identify ~~biomonitering~~ biomonitoring studies of glyphosate were also performed using PubMed. We searched on the terms "glyphosate" and "Round up OR Roundup" in separate searches. Both searches also included the term "biomonitoring" as well as related terms including "sample," "urine," and "blood." Abstracts identified from these searches were reviewed. For all articles of interest, the 'related articles' identified by PubMed were also reviewed. All relevant articles were obtained.

For completeness, we examined the reference sections of the primary epidemiology and biomonitoring publications for additional articles that may not have been identified by the PubMed searches.

Studies were included in our review if they met the following criteria:

- Published in peer-reviewed journal
- English language

- For studies of health outcomes, must be epidemiologic studies (e.g., cohort, case-control)
    - Epidemiologic studies must have evaluated the association between glyphosate and cancer or non-cancer health outcome(s); analyses of more general categories of "pesticides" or "herbicides" did not meet our criteria

Studies of poisonings or other acute effects of glyphosate were not included.

Results

Cancer Outcomes

Cohort Studies. Five cohort studies evaluated the association between glyphosate and at least one type of cancer. Brief descriptions of each study are presented in Table 1. One cohort study evaluated multiple pesticides and multiple cancer sites in children (Flower et al. 2004), one study examined glyphosate and multiple cancer sites (De Roos et al. 2003), and three studies evaluated multiple pesticides and site-specific cancers, including prostate (Alavanja et al. 2003), colon/rectum (Lee et al. 2007), and breast (Engel et al. 2005). All of these analyses were conducted among participants or family members of the Agricultural Health Study (AHS) cohort. The AHS is a prospective study of private and commercial applicators in Iowa and North Carolina. Participants were asked to complete a 21-page questionnaire that included data on personally mixing and/or applying glyphosate, and frequency (days of use per year) and duration (years of use) of glyphosate use. Data on the use of personal protective equipment, other farming

practices, dietary and lifestyle information, demographic data and medical information were also collected via questionnaire.

Main results of the cohort studies reporting data on glyphosate and cancer are shown in Table 2. Flower et al. (2004) evaluated associations between parental pesticide application and childhood cancer among children born to Iowa participants in the AHS. Female applicators and spouses of male applicators were asked to complete a questionnaire on children born after 1975. This information was used to conduct a linkage with the Iowa Cancer Registry to identify cases of cancer among children age 19 and younger, diagnosed between 1975 and 1998. The linkage identified 50 childhood cancer cases. Glyphosate exposure was determined by self-reported responses to questionnaires completed by applicators and spouses. There was no association between maternal (OR = 0.61; 95% CI: 0.32-1.16) or paternal (OR = 0.84; 95% CI: 0.35-2.34) use of glyphosate and risk of childhood cancer.

De Roos et al. (2005a) evaluated associations between glyphosate exposure and incidence of total and specific cancers in the AHS. There was no significant association between glyphosate and "all cancers" or any cancer site in analyses of ever versus never exposure to glyphosate, analyses of tertiles of cumulative exposure days of glyphosate exposure, or in analyses of tertiles of intensity-weighted exposure days. Results for analyses of tertiles were reported for the models that excluded never-exposed participants and used the lowest-exposed category as the reference group. Intensity levels were estimated based on questionnaire responses using the following algorithm: intensity level = [(mixing status

+ application method + equipment repair status) x personal protective equipment use] (De Roos et al. 2005a). The authors stated that they considered p-values less than 0.10 as being indicative of a trend. There were two p-values that met this criterion, but neither corresponded to monotonic positive patterns of association. In the intensity-weighted analysis of glyphosate and lung cancer, the relative risk for the highest tertile was 0.6 (95% CI: 0.3-1.0) and the corresponding p-value for trend was 0.02. For similar analyses of pancreatic cancer, the relative risk in the highest tertile was 0.5 (95% CI: 0.1-1.9) and the p-value for trend was 0.06. The corresponding relative risk for multiple myeloma was 2.1, but the corresponding 95% confidence interval was wide (0.6-7.0), and the p-value for trend was above the 0.10 threshold (p=0.17). Thus, there was no evidence of a significant *positive* association for any of the cancers for which data were reported. Nevertheless, the authors concluded, "a suggested association between glyphosate and the risk of multiple myeloma" (De Roos et al. 2005a). Lash (2007) examined this association further by using Monte Carlo simulation to conduct an analysis to quantify the bias and uncertainty that may be attributable to systematic (non-random) error. De Roos et al. (2005a) acknowledged in their paper that over 13,000 subjects were excluded from multivariate analyses because of missing data. In analyses of "ever" *versus* "never" exposure to glyphosate, the age-adjusted RR was 1.1, whereas the multivariate-adjusted RR was 2.6 (De Roos et al. 2005a). Lash's results indicated that adjustment for confounders, which resulted in limiting the data set, produced an estimate that was "substantially biased," and that this bias was likely in the direction away from the null (Lash 2007).

Alavanja et al. (2003) evaluated associations between specific pesticides and prostate cancer in the AHS. Glyphosate was listed as one of the herbicides for which information on frequency, duration, intensity and cumulative exposure was available. In the table of results, however, glyphosate was not listed. The authors stated that pesticides for which "no exposure-response association with prostate cancer was observed" were omitted from the results table to save space. Thus, it can be assumed that there was no significant positive association between glyphosate and prostate cancer in this study. In their analysis of colorectal cancer and pesticide use, Lee et al. (2007) found no significant association between glyphosate use (ever versus never) and colorectal cancer overall (RR = 1.2; 95% CI; 0.9-1.6), or cancer of the colon (RR = 1.0; 95% CI: 0.7-1.5) or rectum (RR = 1.6; 0.9-2.9). The authors presented analyses of nine pesticides by increasing category of lifetime exposure days, but results for glyphosate were not reported, presumably because there was nothing remarkable to report. Engel et al. (2005) evaluated breast cancer risk among farmers' wives in the Agricultural Health Studies. The authors analyzed associations of breast cancer incidence with glyphosate use among farmers' wives, with glyphosate use among husbands of wives who never used pesticides. After adjustment for age, race, and state of residence, there was no significant association in either analysis (Table 2). Although the authors presented additional analyses that stratified on state and on menopausal status, results for glyphosate were not reported.

Case-Control Studies. Thirteen case-control studies that analyzed glyphosate exposure and cancer were identified and included in this review (Table 3). There is some overlap among these studies, including pooled analyses, as will be described in the following

paragraphs. Six studies evaluated non-Hodgkin lymphoma (NHL) (Cantor et al. 1992; De Roos et al. 2003; Hardell and Eriksson 1999; Hardell et al. 2002; Lee et al. 2004a; McDuffie et al. 2001), two studies analyzed hairy cell leukemia (Nordstrom et al. 1998; Hardell et al. 2002), three studies evaluated gliomas (Carreon et al. 2005; Lee et al. 2005; Ruder et al. 2004), and there was one published study on each of the following: leukemia (adult males) (Brown et al. 1990), multiple myeloma (Brown et al. 1993), and stomach and esophagus (Lee et al. 2004b). Main results for these studies are shown in Table 4.

Three case-control studies were conducted by the National Cancer Institute in Iowa and Minnesota during the 1980s, utilizing the same control series for each of the three lymphohematopoietic cancers studied. For each study, men reporting glyphosate exposure were compared to nonfarmers. There was no association between glyphosate exposure and leukemia among white males residing in Minnesota and Iowa (OR = 0.9; 95% CI: 0.5–1.6) (Brown et al. 1990). The odds ratio for multiple myeloma was elevated, but not statistically significant, among Iowa farmers reporting ever handling glyphosate (OR = 1.7; 95% CI: 0.8-3.6) (Brown et al. 1993). Cantor et al. (1992) observed no association between glyphosate exposure and NHL among Iowa and Minnesota males (OR = 1.1; 95% CI: 0.7-1.9).

Lee et al. (2004a) pooled data from the Iowa and Minnesota NHL case-control study (Cantor et al. 1992) with a similar case-control study conducted in Nebraska that did not publish data on glyphosate (Zahm et al. 1990). In the pooled analysis, results were stratified on asthma status to examine whether asthma may modify potential associations

between pesticide exposures and NHL. Associations between NHL and glyphosate use among asthmatics and nonasthmatics were not significantly elevated, nor did they differ significantly from each other (OR for asthmatics = 1.2; 95% CI: 0.4-3.3; OR for nonasthmatics = 1.4; 0.98-2.1). De Roos et al. (2003) conducted a pooled logistic regression analysis and hierarchical regression of NHL (in males) and pesticides, including glyphosate, using data from case-control studies conducted in Iowa and Minnesota, Nebraska, and Kansas. The first-level model of the hierarchical regression analysis included simultaneous adjustment for 47 pesticides in addition to age and study site. The second-level model included incorporated data on "prior covariates" or factors that were hypothesized to be related to the individual "true" effects. These factors included indicators of type of pesticide and toxicity, and values were assigned based on IARC and EPA classifications. Glyphosate was assigned a zero for all pesticide covariates (e.g., insecticides, organochlorines, organophosphates) and a carcinogenic probability value of 0.3, which corresponded to "not assessed by IARC or USAPA IRIS, or deemed unclassifiable in one or both assessments." The logistic regression analysis produced a statistically significant odds ratio for ever use of glyphosate (OR = 2.1; 95% CI: 1.1-4.0), whereas the estimate was reduced and no longer statistically significant in the hierarchical regression (OR = 1.6; 95% CI: 0.9-2.8). The data available in this study did not permit analyses of duration or frequency of use.

A Canadian population-based case-control study of NHL in men (n=517 cases) and pesticide exposure found a non-significant positive association between self-reported glyphosate exposure and NHL (multivariate-adjusted OR = 1.20; 95% CI: 0.83-1.74).

Hardell et al. (2002) reported results of a pooled analysis of two Swedish case-control studies: one of NHL, and one of hairy cell leukemia (HCL), which is classified as a type of NHL. The individual studies reported statistically nonsignificant positive associations between glyphosate and NHL (OR adjusted for age and country = 2.3; 95% CI: 0.4-13; multivariate-adjusted OR = 5.8; 95% CI: 0.6-54) (Hardell and Eriksson 1999) and HCL (OR = 3.1; 95% CI: 0.8-12) (Nordstrom et al. 1998). In both studies, estimates were based on few exposed cases (n=4) and corresponding confidence intervals were quite wide (Table 4). The pooled analysis combined NHL and HCL cases (n = 515), and whereas the "univariate" odds ratio was similar that those in the individual studies (OR = 3.04; 95% CI: 1.08-8.52), the multivariate-adjusted odds ratio was attenuated (OR = 1.85; 95% CI: 0.55-6.20) (Hardell et al. 2002).

A case-control study of glioma in Nebraska reported an overall odds ratio of 1.5 (95% CI: 0.7-3.1) for glyphosate exposure (as compared with non-farmers, who were considered "unexposed") (Lee et al. 2005). The odds ratios differed depending on type of respondent (OR for self-respondents = 0.4; OR for proxy respondents = 3.1), and the authors expressed concern that differential misclassification may explain the positive associations observed for proxy respondents for glyphosate and other several other pesticides. The National Institute initiated the Upper Midwest Health Study for Occupational Safety and Health (NIOSH) to evaluate brain cancer among rural residents of four midwestern states. In this study, there was no association between gliomas and glyphosate among women (OR = 0.7; 95% CI: 0.4-1.3) (Carreon et al. 2005). The study investigators did not publish the results for analyses of glyphosate and gliomas in men,

but stated the following about a group of individual pesticides, which included glyphosate: "We observed no statistically significant associations in analyses including and excluding proxy respondents..." (Ruder et al. 2004).

Lee et al. (2004b) conducted a case-control study of stomach and esophageal adenocarcinomas and pesticide use in eastern Nebraska. There was no association between self-reported ever use of glyphosate and either stomach cancer (OR = 0.8; 95% CI: 0.4-1.5) or esophageal cancer (OR = 0.7; 95% CI: 0.3-1.4).

Summary of Results from Studies of Glyphosate Exposure and Cancer. None of the cohort studies reported statistically significant positive findings for glyphosate exposure and total cancer or any site-specific cancer in adults or children. Although the relative risk for multiple myeloma reported by De Roos et al. (2005a) was greater than 2.0 (OR = 2.1), formal bias analysis indicated that this estimate was likely spuriously high as a result of bias (Lash 2007). De Roos et al. (2003) reported a statistically significant association based on a pooled analysis of case-control studies of NHL and glyphosate, but the pooled odds ratio was not significant in the hierarchical regression. Hardell et al. (2002) reported a significant positive univariate association between glyphosate association and NHL, but the multivariate-adjusted odds ratio was attenuated and not statistically significant. Lee et al. (2005) observed a significantly elevated odds ratio between gliomas and glyphosate in analyses restricted to proxy respondents, but analyses of self-respondents and self- and proxy-respondents combined were not statistically significant. Thus, there were no consistent patterns of statistically significant positive

associations between glyphosate and any cancer, nor was there evidence of increasing risk with increasing exposure in studies that had data to analyze exposure-response patterns. Taken together, the epidemiologic data do not support a causal association between glyphosate exposure and cancer.

Non-Cancer Outcomes

Cohort Studies. Although associations between glyphosate and non-cancer outcomes were examined in study cohorts, including the AHS cohort, analyses were based on cross-sectional data (e.g., baseline questionnaire). The one exception to this was the study of pesticides and Parkinson's disease (PD) by Kamel et al. (2007) which analyzed both baseline prevalence data as well as incident PD cases identified during the 1999-2003 follow-up. Because the authors did not conduct a prospective analysis, we reported both the prevalence and incidence findings from this study in the cross-sectional studies section. In addition, one nested case-control study of rheumatoid arthritis (RA) was conducted in the AHS, and is described in the case-control studies section. Accordingly, results from these and other studies are reported in the following sections, which include summaries of case-control and cross-sectional studies that evaluated glyphosate and various non-cancer health conditions.

Case-Control Studies.

We identified and reviewed two case-control studies that evaluated glyphosate and reproductive outcomes (Garcia et al. 1998; Rull et al. 2006), one case-control study evaluating PD (Wechsler et al. 1991), and one nested case-control study of rheumatoid

arthritis (De Roos et al. 2005b). Brief descriptions of each study are presented in Table 5, and results are summarized in Table 6.

In a case-control study conducted in an agricultural region of Spain, Garcia et al. (1998) observed no significant association between fathers' exposure to glyphosate three months prior to conception or during the first trimester of pregnancy and congenital malformations (OR = 0.94; 95% CI: 0.37-2.34). Rull et al. (2006) pooled data from two California case-control studies that evaluated neural tube defects (NTDs) and residential proximity to areas where agricultural pesticides were applied. Results for glyphosate were similar regardless of the statistical model used, and each of the reported 95% confidence intervals included 1.0 (Table 6). In the hierarchical regression model evaluating glyphosate use within 1000 meters of maternal residences and NTDs, the odds ratio was 1.4 and statistically nonsignificant (95% CI: 0.8-2.5).

Wechsler et al. (1991) conducted a pilot case-control study of PD. Data on home use of Round-Up exposure was available for 19 cases (14 exposed) and 22 controls (9 exposed). The unadjusted odds ratio was 4.04, but the corresponding confidence interval was wide and included 1.0 (95% CI: 0.91-19.27). The authors conducted further evaluation, including duration of use, of three home pesticides, but these did not include Round-Up. De Roos et al. (2005b) conducted a nested case-control study of RA within the AHS female cohort. Cases were women with physician-confirmed RA, initially self-reported as part of a 5-year follow-up interview. The authors stated, "Risk of RA was not associated with mixing or applying pesticides overall or with any pesticide class" (De

Comment [d1]: Was this reported as "Round-Up" or "Roundup"?

Roos et al. 2005b). Similarly, there was no significant association between glyphosate exposure and RA (OR = 1.2; 95% CI: 0.8-1.8).

Cross-Sectional Studies.

Brief descriptions of cross-sectional analyses of glyphosate exposure and non-cancer outcomes are presented in Table 7. Five cross-sectional studies evaluated reproductive outcomes (Arbuckle et al. 2001; Curtis et al. 1999; Garry et al. 2002; Saldana et al. 2007; Savitz et al. 1997), five cross-sectional studies analyzed respiratory conditions in the AHS (Hoppin et al. 2008; Hoppin et al. 2007; Hoppin et al. 2006; Hoppin et al. 2002; Valcin et al. 2007), and there was one study each of Parkinson's disease (Kamel et al. 2007) and retinal degeneration (Kirrane et al. 2005). Main results of these studies are shown in Table 8.

Three reports analyzed cross-sectional data from the Ontario Farm Family Health Study. This study identified eligible farm couples and obtained questionnaire data on farm activities and reproductive health. The women in the study were asked to report information on all of their pregnancies. Savitz et al. (1997) evaluated associations between male farm activities and pregnancy outcomes. The odds ratios for miscarriages were similar for glyphosate use on crops and on yards, but neither was statistically significant (OR for glyphosate use on crops = 1.5; 95% CI: 0.8-2.7; OR for glyphosate use in the yard = 1.4; 95% CI: 0.7-2.8). The odds ratio for preterm delivery and glyphosate use on crops was 2.4, but the corresponding 95% confidence interval (0.8-7.9) was wide and included 1.0. There were fewer than 5 preterm delivery cases whose

fathers reported using glyphosate on yards and the authors did not analyze these data further. Arbuckle et al. (2001) conducted an "exploratory analysis" to explore the role of exposure timing for pesticides as potential risk factors for spontaneous abortion. The authors reported a borderline significant association between preconception exposure to glyphosate and spontaneous abortion (OR = 1.4; 95% CI: 1.0-2.1), but no significant association with postconception exposure (OR = 1.1; 95% CI: 0.7-1.7). The authors noted many limitations to this study, including likely exposure misclassification and issues with assigning exposures accurately to the preconception or postconception window. Furthermore, the authors stated, "Because the analyses were designed to generate, not to test, hypotheses, and multiple comparisons were conducted, results should be interpreted with care and tested in other studies" (Arbuckle et al. 2001). Curtis et al. (1999) calculated conditional fecundability ratios (CFR) for several types of pesticides. "Conditional fecundability" is conditional on pregnancy. The CFR estimates the conditional fecundability for the exposed group divided by that of the unexposed group, and a CFR of less than 1.0 indicates a reduced probability of conception in the exposed group, relative to the unexposed (Curtis et al. 1999). The CFR was less than 1.0, but not statistically significant, for the exposure group in which women reported glyphosate regardless of men's use (CFR = 0.61; 95% CI: 0.30-1.26). For the exposure group in which men reported glyphosate use, but there was no use by women, the CFR was 1.30 (95% CI: 1.07-1.56). Self-reported glyphosate exposure during pregnancy was associated inversely with gestational diabetes (crude OR = 0.61; 95% CI: 0.26-1.48; adjusted odds ratios were presented graphically) in a cross-sectional analysis of data from the AHS (Saldana et al. 2007). Garry et al. (2002) conducted a cross-sectional study of

pesticide applicators and their families. The authors evaluated numerous pesticides and several types of birth defects and adverse developmental outcomes. Parent-reported ADD/ADHD in children was associated positively and significantly with use of glyphosate; 6 out of 14 children with parent-reported ADD/ADHD had exposure to phosphonamino herbicides (glyphosate, Roundup) (OR = 3.6; 95% CI: 1.35-9.65). The ADD/ADHD diagnoses were not confirmed by a clinician, however.

There were six published cross-sectional studies of non-cancerous respiratory conditions and glyphosate exposure conducted among participants in the AHS, including one study of asthma (Hoppin et al. 2008), two studies of chronic bronchitis (Hoppin et al. 2007; Valcin et al. 2007), and two studies of wheeze (Hoppin et al. 2006; Hoppin et al. 2002). Hoppin et al. (2008) evaluated associations between pesticide use and self-reported history of doctor-diagnosed asthma among farm women. Atopic asthma was defined as occurring with eczema and/or hay fever. There was a modest, statistically significant, positive association between glyphosate use and atopic asthma (OR = 1.31; 95% CI: 1.02-1.67), but the association with nonatopic asthma was not statistically significant (OR = 1.13; 95% CI: 0.92-1.39), nor was the difference between these two odds ratios statistically significant (p-value for difference = 0.337). The odds ratio for the association between glyphosate and atopy alone (i.e., doctor diagnosis of eczema or hay fever) was similar to that of atopic asthma (OR for atopy alone = 1.31; 95% CI: 1.21-1.42; OR for atopic asthma = 1.35; 95% CI: 1.05-1.73). Hoppin et al. (2007) evaluated associations between pesticides and self-reported doctor-diagnosed chronic bronchitis (after age 19) among farmers, whereas Valcin et al. (2007) evaluated a similar association

among non-smoking farm women in the AHS. Both analyses produced odds ratios of approximately 1.0 (or slightly below 1.0) for lifetime exposure to glyphosate (OR for farmers (94% male) = 0.99; 95% CI: 0.82-1.19 (Hoppin et al. 2007); OR for non-smoking farm women = 0.94; 95% CI: 0.76-1.17 (Valcin et al. 2007)). Hoppin et al. (2002, 2006) evaluated pesticide use and wheeze, which was defined based on responses to the question, "How many episodes of wheezing or whistling in your chest have you had in the past 12 months?" There was no significant association between glyphosate exposure and wheeze in analyses of farmers (OR = 1.05; 95% CI: 0.95-1.17) or commercial applicators (OR = 1.14; 95% CI: 0.83-1.57) (Hoppin et al. 2002; Hoppin et al. 2006, respectively).

Kamel et al. (2007) observed no association between glyphosate use and self-reported PD in analyses of prevalent PD cases (OR = 1.0; 95% CI: 0.6-1.7) and incident cases (OR = 1.1; 95% CI: 0.6-2.0). In an analysis of pesticides and self-reported, doctor-diagnosed retinal or macular degeneration among wives of pesticide applicators in the AHS, Kirrane et al. (2005) observed no association between glyphosate and these conditions (OR = 1.1; 95% CI: 0.8-1.5).

Summary of Results from Studies of Glyphosate Exposure and Non-Cancer Health Outcomes. Case-control and cross-sectional studies on glyphosate and reproductive outcomes evaluated a variety of endpoints and most studies observed no significant positive association, regardless of the outcome evaluated. Garry et al. (2002) conducted multiple analyses and observed a significant positive association between parental use of

glyphosate and parent-reported ADD/ADHD in children, but the diagnosis was not confirmed by a clinician. In a series of cross-sectional analyses of data from the AHS, glyphosate exposure was not associated significantly with chronic bronchitis (Hoppin et al. 2007; Valcin et al. 2007), wheeze (Hoppin et al. 2002; Hoppin et al. 2006), or non-atopic asthma (Hoppin et al. 2008). The positive association with atopic asthma was similar in magnitude to the association with atopy alone (Hoppin et al. 2008). Finally, there were no statistically significant positive associations with the other health outcomes evaluated, including Parkinson's disease (Wechsler et al. 1991; Kamel et al. 2007), retinal degeneration (Kirrane et al. 2005), or rheumatoid arthritis (De Roos et al. 2005b). Thus, data from epidemiologic studies do not support a causal association between glyphosate and any of the adverse health outcomes evaluated to date.

Biomonitoring Studies

The validity of epidemiologic studies that evaluate the relationship of exposure to environmental chemicals, including glyphosate, and adverse health effects will depend in large part on the ability to correctly quantify and classify an individual's exposure. Instruments for exposure assessment include interviews and questionnaires, measurements in the macroenvironment (e.g., chemicals in municipal water supply), measurements of the microenvironment (e.g., chemicals coming out of home water tap), individual doses (e.g., measurements with personal air monitors), measurements in human tissues or products, and markers of physiological effects (Hertz-Picciotto 1998). All of the studies in the previous sections have relied primarily on questionnaires and interviews to characterize glyphosate exposure among participants. Environmental and

ecologic monitoring data are useful to identify the sources of exposure; however a full assessment of the environmental monitoring of exposure may not capture all contributing exposures nor accurately reflect an individual's absorbed dose (Barr et al. 1999). Biomonitoring defines exposure through the absorbed, or internal, dose (Calafat et al. 2006) by measuring biomarkers in body products such as blood, urine and tissue. The biologic samples reflect the cumulative exposure for all sources and routes (Albertini et al. 2006; Calafat et al. 2006). The following section describes biomonitoring studies of glyphosate.

The first published study of biologic monitoring for glyphosate was of 14 conifer seedling nursery workers exposed to glyphosate who were monitored to quantitate the absorbed dose (Lavy et al 1992). Exposure was characterized using passive dosimetry (dislodged residue from conifer seedlings, gauze patches (9 per worker), and hand rinses at the end of each day) and active biological monitoring methods (urine). This study found only one sample with dislodged residue from conifer seedlings, a measurable amount on most patches and hand washes, and no positive urine samples. These results were explained by high rainfall, normal field dissipation, and worker training concluding that glyphosate is not indicated to pose a threat under normal nursery conditions. Another study of pesticide exposure evaluated multi-pesticide exposure in 73 nursery-workers (Lavy et al. 1993); 17 pesticides including glyphosate were studied. Exposure to these pesticides was assessed using dislodged pesticide residues, gauze patches, hand rinses, and biological monitoring (urine) during the spray season lasting from March 1986 through February 1987. This study found 8.3% of the dislodged residue samples

had detectable quantities of pesticide, followed by patch samples (3.2%), handrinse (2.9%), and urine samples (1.3%); over 6,000 samples were tested for each of the sample types. Jauhiainen et al. (1991) conducted a study of forest workers exposed to glyphosate during use with pressurized sprayers. Case and control groups of 5 participants each in northeastern Finland were medically examined one week before and one week after a 1-week working period in August 1988. Air samples were collected within the breathing zone of the workers and urine samples were collected at the end of each day. The glyphosate levels measured in the air samples were low. All urine samples were below the detection limit of the instrumentation. Most recently, a study in Iowa investigated agricultural pesticides exposure among 25 farm and 25 non-farm households, including pesticide contamination inside homes (Curwin et al. 2007). Samples were collected between May and August of 2001, 1-5 days after pesticide application and approximately 4 weeks later; at both sampling times 2 spot urine samples were collected. Four different pesticides were analyzed, including glyphosate. Additional information was collected using a questionnaire. This study evaluated the correlation of passive and active exposure assessment with the intention of validating the passive system to save the time, effort, and cost of active exposure assessments. However, no glyphosate was detected in the urine of any of the samples, thus no correlation could be made. Through considerations of 'postulated data (half of the lower limit of method validation)' for the biomonitoring results, the passive monitoring data was determined to be an over-estimate of exposure by at least 11-fold for the more highly exposed participants. As limits of detection continue to decrease, biomonitoring values will be quantified more accurately.

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The Farm Family Exposure Study (FFES), a biomonitoring study conducted in South Carolina and Minnesota, evaluated pesticide exposures among farmers, farmers' spouses, and their children before, during, and after application (Acquavella et al. 2004; Mandel et al. 2005; Baker et al. 2005). Because epidemiologic studies rely on self-reported exposure data, this biomonitoring study provided a resource for evaluating models of pesticide exposure and for developing predictors of exposure intensity for future epidemiologic studies. Participants were recruited by random selection of licensed pesticide applicators available from state listings. Selected participants were first contacted by a letter and then by phone to assess eligibility and interest in participation. Eligibility criteria included: 1) the farmer, spouse, and at least one child between the ages of 4-18 years had to live on the farm: 2) they had to farm at least 10 acres, and that land needed to be within one mile of the family residence; 3) the farmer needed to have plans to apply glyphosate, 2,4-dicholophenoxyacetic acid (2,4-D), and/or chlorpyrifos to the land; 4) family members had to agree to five consecutive days of personal urine sample collections (one day before, three days during, and one day after pesticide application); and 5) the farmer and spouse had to agree to fill out pre- and post- family activity; questionnaires (detailing the week before and the week of the study) and to have trained field staff observe their pesticide application practices. A total of 11,164 applicators were screened from a list of 36,106 licensed pesticide applicators. In all, 994 farm families were eligible to participate in the study and 95 farm families were enrolled. Field staff observed pesticide applications and recorded information such as meteorological conditions, work practices, and family activity patterns relevant to exposure potential. Samples were tested and corrected for previously determined

laboratory analytical recovery and storage stability. Forty-eight participating farm families were exposed to glyphosate (Acquavella et al. 2004). Systemic dose was calculated for all participants with a detectible level of glyphosate in their urine by calculating the quantity excreted during the study period, adjusting for incomplete excretion (the residual amount of glyphosate that would have been excreted had urine samples been collected until all systemically available glyphosate was eliminated), adjusting for pharmacokinetic recovery (based on the percent glyphosate recovered when administered intravenously into monkeys), and dividing this value by the participants body weight. Overall, the highest urine pesticide concentrations were detected in applicators; children had much lower levels and spouses had the lowest. Acquavella et al (2004) reported 60% of the farmers had detectable levels of glyphosate in their urine on the day of application. The geometric mean was 5-fold higher in applicators reporting not wearing gloves. For children, 12% had detectable levels in their urine; all but one of these helped with the mixing, loading, or application of the pesticide. None of the calculated systemic doses reached the U.S. Environmental Protection Agency reference dose for glyphosate. Mandel et al. (2005) showed that exposure profiles differed for the three chemicals and emphasized the importance of chemical-specific considerations when using exposure assessment in biomonitoring studies. Factors to consider in this study are that the data were obtained from a one time sampling of one application per family, the application of glyphosate was by tractor and boom in all cases, which may not be representative of other exposure sources, participation in the study may have changed behaviors and introduced biases, for example the use of personal protection equipment

and selection bias may have occurred due to the requirement for extensive collection of urine samples.

In a letter to the editor, concern was expressed regarding the normalization of the serum creatinine measurements, as well as the uncorrected detectable levels of glyphosate found at the beginning of this study and the one time sampling scheme (Mage 2006). In response to this letter, Acquavella et al. (2006a) stated that the normalization of the serum creatinine measurements could have been reported as micrograms per deciliter instead of micrograms per day, but nonetheless only four samples were below the lower end of the normal range; thus the completeness of the urine collection was exceptional. Second, the uncorrected detectable levels of glyphosate found at the beginning of this study were included in the final values for epidemiologic and public health significance to know to determine the total dose during and after application. In addition, the inclusions of these baseline values were insignificant because the highest systemic dose estimated in the study (0.004 mg/kg/day) was already almost three-fold less than the EPA reference dose (1.75 mg/kg/day). Finally, regarding the one-time sampling scheme, the authors commented that the objective for the FFES was to "quantify real-world pesticide exposure immediately before, during and after a pesticide application" (Acquavella et al. 2004). Thus, although characterizing exposure over many seasons would provide valuable information, it was not the objective of the study. In addition, the FFES assessed exposure in farm families to a greater extent than previous studies.

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Other exposure assessment tools

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Other tools used for exposure characterization have included proxy measures such as occupation or residence, dosimetry (measuring the amount of pesticide deposited on clothing, skin, and in the breathing zone through dermal patches, handwipes, air sampling), and questionnaires. Although these methods have been used to quantify exposure, uncertainties of these methods can contribute to discrepant risk estimates. Job title has also been used as a proxy exposure for pesticides, but does not account for type and magnitude of exposure. Living on a farm has also been used, but specific exposure to a pesticide is most likely related to more direct contact through loading, mixing or applying the material, or being in close proximity to an application. Dosimetry provides information of specific routes of exposure and exposure information directly related to a particular activity (Barr et al. 2006). Dosimetry measures potential exposure, however, and not actual internal dose (Barr et al. 2006). Questionnaires are commonly used for exposure characterization and capture self-reported exposure data. This is cost-efficient and non-invasive, but is subject to misclassification and recall bias. Hoppin et al (2002) evaluated the validity of reported pesticide use from participants of the AHS based on years the pesticide was officially registered and concluded the participants provided plausible information regarding pesticide use. This was explained as a combination of good recall and broad definitions of analytic categories. In a study by Blair and Zahm (1993) evaluating the self-reported use of pesticides with information provided by major suppliers, an agreement was found 60% of the time for both cases and controls (nondifferential). Differential bias is a general concern due to recall bias in cases, but that was not found to be an issue in this study. Acquavella et al (2006b) evaluated an algorithm used to estimate lifetime average exposure intensity (Dosemeci et al. 2002)

based on responses to a questionnaire against measured urinary pesticide concentrations. The study found low to moderate correlations between trained field observers' assessments and urine concentrations for specific pesticides (Spearman correlations ranged from 0.12-0.47) and lower correlations with participant's self reports and urine concentrations (Spearman correlations ranged from 0.13-0.25). For glyphosate, evaluation of participant's self-reports and systemic dose resulted in essentially no correlation (Spearman correlation = 0.04). In addition, this study reported contrasting correlations when evaluating different formulations of the same pesticide to urinary pesticide concentrations. The discussion emphasized the importance of incorporating not only duration and frequency of pesticide use, but also type of pesticide formulation into exposure characterizations. The specific physical and chemical properties, formulations, and application practices of the individual pesticide lead to different toxicokinetic properties. Thus, generic exposure assessments likely lead to exposure misclassification, and all exposure algorithms should be validated with biomonitoring data.

Discussion

Our review of the epidemiologic literature on glyphosate and cancer and non-cancer health outcomes found no evidence of a consistent pattern of positive associations indicating a causal relationship between any disease and exposure to glyphosate. The prospective AHS has evaluated associations between glyphosate and all cancer sites (De Roos et al. 2005a), with no statistically significant results. Cross-sectional analyses of other health endpoints in this cohort have produced similar results. Other studies, including case-control studies of specific cancers and other cross-sectional studies of

reproductive outcomes have similarly reported results consistent with the null hypothesis. These results are not surprising, given that glyphosate has been classified as a noncarcinogenic and non-mutagenic chemical (WHO 1994).

Biomonitoring studies have generally found low levels of glyphosate in urine, or levels below the detection limit of the instrumentation (e.g., Jauhiainen et al. 1991; Curwin et al. 2007). The FFES found detectable levels of glyphosate in the urine of 60% of farmers on the day of application, but in only 3% of spouses and 12% of children. None of the participants' systemic doses approached the US EPA reference dose for glyphosate.

Biomonitoring studies can be useful not only in estimating systemic dose, but also in validating other exposure assessment tools, such as questionnaires. Indeed, Acquavella et al. (2006b) used data from the FFES to evaluate the exposure intensity algorithm used in the AHS and found generally low to moderate correlations.

In conclusion, the collection of epidemiologic studies of glyphosate to date indicates that glyphosate is not causally related to the reproductive or chronic health outcomes studied.

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