CENTER FOR FOOD SAFETY

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RE: Docket EPA-HQ-OPP-2016-0385

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Panel members have a huge amount of material to assess, and limited time. To ease your task, I will first summarize my comments by section number so that those who wish to examine certain issues in more detail but not others can go directly to the full treatment. I address:

Section 1: Epidemiology
Section 2: Analysis and interpretation of animal data
Section 3: Rat studies
Section 4: Mouse studies
Section 5: Carcinogenic potential in animals
Section 6: Overall assessment of carcinogenic potential

I do not discuss the mechanistic evidence. The EPA's Glyphosate Issue Paper: Evaluation of Carcinogenic Potential is referenced as EPA (2016), and the Agency's 2005 Guidelines for Carcinogen Risk Assessment as EPA (2005) or EPA Guidelines. I also refer to materials in the SAP docket (EPA-HQ-OPP-2016-0385)[1] as well as other EPA reviews and memoranda, which for simplicity's sake are referenced by date, e.g. EPA (2/9/82). A full list of references is provided at the end. Many documents I reference here are being submitted to the SAP docket under filenames that match the in-text citations (e.g. NRC 1987) for those who wish to examine them. I would also be happy to provide any materials via email.

[1] https://www.regulations.gov/searchResults?rpp=25&so=ASC&sb=title&po=100&s=epa-hQ-OPP-2016-0385&dct=FR%2BPR%2BN%2BO%2BSR.

Summary

Section

1.0 EPIDEMIOLOGY

1.1 NHL and farmers: Epidemiology studies consistently find an elevated rate of non-Hodgkin's lymphoma in farmers, though farmers have lower rates of cancer overall.

1.2 NHL and glyphosate exposure: Higher glyphosate usage rates and hence increased farmer exposure in the 1980s correlate with higher estimates of NHL risk in epidemiology studies conducted then.

1.3 Assessment of epidemiology: A properly ***graded*** assessment of the human data shows that a causal relationship between glyphosate exposure and NHL is credible, even if chance or bias cannot be definitively ruled out.

2.0 ANALYSIS AND INTERPRETATION OF ANIMAL DATA

2.1 Dose selection: EPA mischaracterizes its carcinogen test guidelines as setting a "limit dose" of 1,000 mg/kg/day, when in fact this serves as the ***minimum*** high-dose level when doses exceeding it do not elicit signs of toxicity; 5% of feed is the "practical upper limit" for dietary studies, and this limit is not exceeded in any study.

2.2 Interpretation of high-dose findings: EPA mistakenly discounts animal tumors at doses ≥ 1,000 mg/kg/day because they exceed human exposure levels. But the high dose is set to maximize power to detect carcinogenic effects, especially rare tumors, not mimic human exposure, so high-dose results must be given full weight.

2.3 Statistical evaluation: EPA frequently demands monotonic dose-response as a criterion of statistical significance, which directly contradicts its Guidelines, which demand only either significant trend (Cochran-Armitage) ***or*** significant pairwise comparison (Fischer Exact)

2.4 Use of historical control data: EPA uses historical controls in a biased manner, only to discount but never support the significance of tumors in treatment groups. The ***mean*** tumor incidence of ***pooled*** historical controls provides the most accurate measure of spontaneous lesions, and should be the preferred comparison standard.

3.0 RAT STUDIES

3.1 Burnett et al., 1979 should be disregarded because it involved administration of a glyphosate ***contaminant*** (N-nitroso-glyphosate) rather than glyphosate.

3.2 EPA improperly dismissed strong evidence of testicular tumors in SD rats in Lankas, 1981 based on lack of monotonic dose-response and faulty interpretation of historical control data. A high incidence of lymphocytic hyperplasia was observed in all female treatment groups, despite the low doses administered in this study.

3.3 In Stout and Ruecker, 1990, EPA improperly discounted significant increases in pancreatic and liver tumors (males) and thyroid C-cell tumors (females) in SD rats based on the faulty premise of an "excessive" high dose.

3.4 In Atkinson et al, 1993a, there was a high incidence of tumors in SD rats, with double the incidence of malignant tumors in high-dose vs. control males. Glyphosate-treated males also exhibited prostate tumors and haemangiosarcomas, which are rare in SD rats. Fuller reporting of tumor data is needed for an adequate review by the SAP.

3.5 In Brammer, 2001, EPA improperly discounted a significant trend of increased liver adenomas in males Wistar rats based on the faulty premises of "excessive" dose and lack of monotonic dose-response.

3.6 Pavkov and Wyand, 1987 should be rejected for two reasons: 1) The doses are too low to adequately test for carcinogenicity; 2) The compound tested is sulfosate, which has different toxicological properties than, and which EPA regulated separately from, all other salts of glyphosate. EPA de-registered sulfosate in 2004, and it is no longer used.

3.7 In Suresh, 1996, no treatment-related increases in tumor incidence were reported in Wistar rats. However, the lack of treatment effects on body weight gain, food consumption, clinical signs or survival suggested that the maximal tolerated dose (MTD) was not achieved.

3.8 In Enemoto, 1997, EPA did not discuss a possible treatment-related increase in lung tumors, which are quite rare in Sprague-Dawley rats. There was no effect of dosage on survival, but signs of toxicity suggest an MTD was achieved.

3.9 In Wood et al. 2009a, there was a highly significant trend in combined incidence of mammary adenomas and adenocarcinomas in female CD-1 mice, sufficient to rule out chance as responsible. There was no effect on survival, and no clinical signs suggesting that an MTD had been reached were reported.

3.10 Review of rat studies: Two of nine should be rejected (see 3.1 & 3.6). Of the remaining seven, four (3.2, 3.3, 3.5, 3.9) and possibly five (3.8) provided significant evidence of neoplasms, including two reporting liver tumors (3.3, 3.5). Rejection of high-dose results in illegitimate. Fuller reporting on 3.4 is needed; 3.7 did not reach an MTD.

4.0 MOUSE STUDIES

4.1 Reyna and Gordon, 1973, conducted at Industrial Bio-Test Laboratories (IBT), should be excluded from SAP review. It is "non-guideline" (2 not 3 doses; high-dose far too low; too few animals examined). In addition, an EPA review of IBT studies in 1983 suggests that this study was found to be "invalid."

4.2 In Knezevich and Hogan, 1983, a CD-1 mouse study, the original finding of a statistically significant increase in renal tubule tumors was dismissed based on the subsequent and disputed finding by a Monsanto consultant of an adenoma in one control mouse kidney. Greim et al (2015) report that no renal tubule adenomas were observed in the concurrent control group in this study. EPA fails to assess historical control data from the performing lab and other sources demonstrating the rarity of this tumor in CD-1 mice. EPA improperly dismisses high-dose tumor findings despite the lack of treatment-related toxic signs or effects on survival. Monsanto exerted undue influence on the interpretation of this study, prevailing over Agency scientists in assessment of the control mouse kidney, use of historical control data, and potentially through the Pathology Working Group.

4.3 In Atkinson et al. 1993b, a highly significant trend of haemangiosarcomas was found in male CD-1 mice; multiple tumors in individual mice and their presence in females as well support this finding. EPA does not report historical control data, but other sources suggest that haemangiosarcomas are quite uncommon in CD-1 mice.

4.4 In this 18-month CD-1 mouse study by Wood et al. 2009b, there was a highly significant and monotonic trend in incidence of malignant lymphomas in male CD-1 mice, and no sign an MTD was reached at the high dose. No historical control data from the performing lab were reported, but properly interpreted data from another lab support the conclusion that the lymphomas were compound-related.

4.5 In Sugimoto, 1997, an 18-month study in CD-1 mice, EPA dismisses a significant monotonic trend for hemangiomas in female mice. EPA did not discuss significant trends in males for malignant lymphomas, renal adenomas and haemangiosarcomas. The high dose was not excessive, as there were no treatment-related effects on mortality.

4.6 Pavkov and Turnier, 1987 should be rejected because the compound tested is sulfosate, which has different toxicological properties than, and which EPA regulated separately from, all other salts of glyphosate. EPA de-registered sulfosate in 2004.

4.7 In Kumar, 2001, an 18-month Swiss albino mouse study, significant trends in males were found for malignant lymphomas and renal cell adenomas. EPA improperly excluded this study based on speculation about a viral infection, for which no evidence is presented.

4.8 Review of mouse studies: Two of six should be rejected (see 4.1 & 4.6), and 4.7 evaluated. Of these five studies, significant kidney tumor findings were made in three (4.2, 4.5, 4.7). Two studies showed statistically increased incidence of haemangiosarcomas in males (4.3, 4.5), supported by presence in females (4.3). Three studies found significantly increased incidence of malignant lymphomas in males (4.4, 4.5, 4.7).

5.0 CARCINOGENIC POTENTIAL IN ANIMALS

A Guideline-based assessment of the animal data, including tumor findings not assessed by EPA, provides sufficient evidence to establish a causal relationship between glyphosate exposure and increased incidence of tumors in multiple tissues. EPA's dismissal of high-dose findings based on comparisons to human exposure levels is not supported by its Guidelines and is entirely inappropriate.

6.0 OVERALL ASSESSMENT OF CARCINOGENIC POTENTIAL

Human epidemiology provides plausible evidence that glyphosate exposure is causally associated with increased incidence of non-Hodgkin lymphoma, even if chance/bias cannot be definitively excluded. According to EPA Guidelines, the concordant malignant lymphoma findings in animal studies "strengthen the weight of evidence of human carcinogenicity." The Guidelines also support a ***hazard*** classification of glyphosate as "likely to be carcinogenic to humans." Many pesticides that EPA deems "likely" human carcinogens continue to be widely used in the U.S. Whether or not glyphosate poses a carcinogenic ***risk*** as well can only be determined after integration of full dose-response and human exposure assessments. EPA calculated a preliminary cancer slope factor for glyphosate in 1985, and an NRC committee estimated oncogenic risk from dietary exposure to glyphosate in 1987. Dietary exposure has increased considerably since that time.

1.0 EPIDEMIOLOGY

1.1 NHL and farmers

A large number of studies and meta-analyses confirm that farmers have a higher incidence of non-Hodgkin's lymphoma than the general population, both in the U.S. and other developed countries (e.g. Keller-Byrne et al. 1997, Khuder et al. 1998, Mannetje et al. 2016). Epidemiologists find this association striking in light of farmers' lower mortality from most cancers, and all cancers combined (Blair and Zahm 1995). Numerous epidemiological studies have been stimulated by the desire to elucidate which factors in farming life might be responsible for this elevated incidence of NHL.

According to the National Cancer Institute, NHL is the seventh most common cancer in the U.S.; 570,000 Americans were living with NHL in 2013; and there will be an estimated 72,500 new

cases of and 20,150 deaths from NHL in 2016 (NCI 2016). According to the American Cancer Society (2016), general symptoms of NHL include unexplained weight loss, fever, drenching night sweats and fatigue. Because NHL can strike different organs, other symptoms vary. Lymphomas in the intestines can block bowel movements, causing pain, nausea or vomiting; or cause perforations in the intestinal wall, allowing gut contents to leak into the abdominal cavity, leading to serious infections with severe pain, nausea and vomiting. Lymphomas in the chest may press on the trachea, causing coughing or breathing difficulties; or obstruct the superior vena cava, causing blood to back up in the veins, which leads to swelling and a bluish-red color in the head, arms and upper chest, a condition that can be life-threatening. Lymphomas affecting the brain cause headaches, trouble thinking, body weakness, personality changes and sometimes seizures. Lymphomas of the skin often appear as extremely itchy, red or purple lumps or nodules under the skin. Lymphoma cells in the blood marrow can suppress blood cell counts leading to severe or frequent infections, easy bruising or bleeding, and anemia. Chemotherapy or radiation therapy to treat NHL, like any cancer, also has numerous, often severe and painful, side effects.

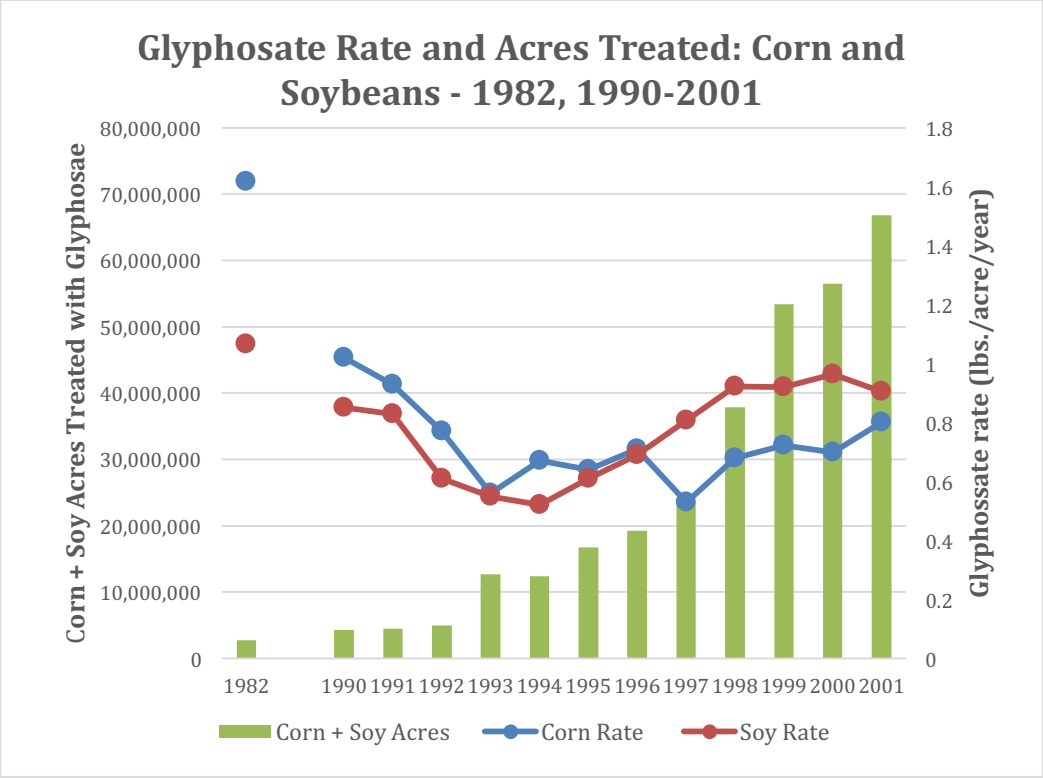
1.2 NHL and glyphosate exposure

In its review of epidemiology studies, EPA argues that if glyphosate exposure is truly associated with NHL, then the risk estimates in ***later*** epidemiology studies should be higher than those in ***earlier*** studies, given the strongly increasing use of glyphosate in U.S. agriculture since the introduction of glyphosate-resistant crops in 1996. That the highest risk estimates are in fact found in the older studies argues against glyphosate as a cause of NHL (EPA 2016, pp. 66-67). Let's take a closer look at this issue.

EPA's hypothesis relies heavily on the notion that rising use of glyphosate at the national level implies a corresponding increase in the exposure of individual, glyphosate-using farmers. EPA assumes that exposure level correlates with usage rate (lbs/acre/year). The other factor driving increased glyphosate use – additional acres treated, which represents an increasing number of "new users" – does not support its hypothesis, because risk estimates are based on the ***proportion*** of glyphosate-using farmers who contract NHL (relative to the proportion of unexposed controls), not on the total number who use it. Thus, one would only expect later epidemiology studies to yield higher risk estimates than earlier ones if it can be demonstrated that farmers in the later studies are exposed to higher levels of glyphosate than farmers in the earlier studies. There are data available to assess this question.

EPA identifies De Roos et al. (2003) as an early study with a high risk estimate (adjusted OR = 2.1, 95% CI=1.1-4.0, logistic regression controlling for co-exposure to other pesticides) (EPA 2016, p. 56). This study acquired cases from Nebraska, Iowa, Minnesota and Kansas from 1979 to 1986. EPA singles out De Roos et al. (2005) as a later study in which "adjusted risk measures were lower (1.0-1.51)." This study recruited applicators from Iowa and North Carolina from 1993 to 1997, with NHL cases identified through the end of 2001 and a median follow-up time of 6.7 years.

In the graph below, glyphosate usage rates for corn and soybeans are plotted against the combined corn/soybean acreage treated with glyphosate in 1982 and from 1990-2001, based on USDA data from Benbrook (2016, Table S6) as well as USDA's annual Agricultural Chemical Use surveys. USDA collected pesticide usage information only sporadically prior to 1990, when it began the annual surveys. Corn and soybeans were chosen as high-acreage crops with increasing use of glyphosate that are also widely grown by farmers in the states covered by the two studies. Usage rate (lbs/acre/year) serves as a proxy for exposure, acres treated as a proxy for number of glyphosate-using farmers.



Sources: USDA NASS (1991-2002); USDA NASS (2016); Benbrook (2016, Table S6).
https://www.nass.usda.gov/Surveys/Guide_to_NASS_Surveys/Chemical_Use/index.php

The most intensive use of glyphosate in the years covered occurred in 1982, with average rates for corn and soybeans of 1.62 and 1.07 lbs/acre/year, respectively. More data for this period would be desirable, but the continuing relatively high rates for 1990 and 1991 (~ 0.9 lbs/acre/year) also suggest that glyphosate was applied quite intensively in the period covered by the De Roos et al (2003) study (1979-1986). In contrast, glyphosate intensity was considerably lower (0.6 to 0.9 lbs/acre/year) in the 1993-2011 period covered by De Roos et al (2005). In addition, the more than five-fold growth in glyphosate-treated corn/soy area during the years of De Roos et al. (2005) – 12.7 to 66.8 million acres from 1993 to 2001 – was the predominant factor driving overall increase in glyphosate use – not, as EPA mistakenly assumes, increasing rates of use by pre-existing users.

Thus, EPA's notion that lower risk estimates in later epidemiology studies argues against glyphosate as a cause of NHL is mistaken. In fact, the greater intensity of glyphosate use by those farmers who applied it during the 1980s, when risk estimates were higher, is consistent with and supports the hypothesis that glyphosate exposure is one risk factor for NHL.

One point deserves emphasis. None of the U.S.-based epidemiological studies addressing glyphosate and NHL covered in this review are based on incident data later than 2001. The few studies with later dates that might appear to either re-analyze previous data (e.g. meta-analyses), or they were conducted outside the U.S. Over the past 15 years for which we lack epidemiological assessment, glyphosate use has increased dramatically. Average rates have risen again to near 1982 levels: 1.40 lbs/acre/year for soybeans (USDA NASS 2015) and 0.99 lbs/acre/year for corn (USDA NASS 2014); and of course many more farmers are being exposed today. Because EPA's hypothesis that more intensive use/exposure leads to higher risk estimates appears to be borne out by De Roos et al. (2003), there may well be an increasing incidence of NHL among farmers that is still awaiting discovery.

We should note that EPA's presentation of glyphosate use in agriculture (EPA 2016, pp. 16-18) appears to have been driven by its desire to discount the epidemiology data. Two examples. First, EPA states: "The increased use of glyphosate may be partly attributed to an increase in the number of famers using glyphosate; ***however, it is more likely that individuals already using glyphosate increased their use and subsequent exposure***" (p. 16, emphasis added). The data that we presented above – which show clearly that increased use is due primarily to the dramatic rise in glyphosate-treated acres (i.e. more farmers spraying it) rather than pre-existing users spraying more intensively – are obviously available to our nation's pesticide regulator. So are the usage rate data. EPA makes routine use of USDA's Agricultural Chemical Use surveys, which regularly report rate of use, percent crop area treated and other data for all major pesticides and all major crops. For one example, see EPA (12/6/12).

Second, EPA states: "Maps from the United States Geological Survey (USGS) displaying glyphosate use in the United States indicate that although use has drastically increased since 1994, ***areas treated with glyphosate for agricultural purposes appear to be approximately the same over time*** (Figures 1.3-1.4)" (p. 16, emphasis added). The fact that glyphosate is used in roughly the same ***regions of the country*** ("areas," not "area") today as it was in 1994 says absolutely nothing about 1) total acres treated; or 2) number of farmers applying it in any given part of the country. The color intensity represents lbs/square mile. A light color means less area treated by fewer farmers, while a darker color means a larger area sprayed by more farmers.[2] EPA's presentation of these maps may create the false impression for some of pre-existing glyphosate users increasing their intensity of use and exposure, which formed the basis of EPA's flawed case against the epidemiology showing an association between glyphosate exposure and NHL.

[2] Usage rates can also be a factor, but as indicated in the graph above, a minor one in comparison to acres treated.

1.3 Assessment of epidemiology

With respect to NHL, three meta-analyses yielded odds ratios of 1.5 (Schinasi and Leon 2014), 1.3 (IARC), and 1.3 (Chang and Delzell 2016), all with lower-bound confidence intervals at 1.0 or above. De Roos et al. (2003)'s integrative assessment of three studies yielded among the highest odds ratios (OR = 2.1 (CI = 1.1-2.0)) controlling for co-exposure to other pesticides (EPA 2016, p. 56). The higher risk estimates in De Roos et al. (2003) accord with higher glyphosate usage rates/exposure in the 1980s. While not all studies agree, the weight of the human evidence demonstrates a plausible causal relationship between glyphosate exposure and NHL, even if chance/bias cannot be definitively ruled out.

It appears that EPA dismisses this evidence because it "cannot exclude chance and/or bias" (EPA 2016, p. 68). With this excessively strict standard, one could dismiss positive findings of many epidemiology studies of even strong carcinogens, given the real-world limitations inherent to the study of uncontrolled human populations. EPA Guidelines call for assessing "the strength of the epidemiological evidence" (EPA 2005, p. 2-4), which implies placing it somewhere along a continuum rather than asking it to provide a yes or no answer. IARC provides a useful model. It has defined four categories for human data: sufficient, limited or inadequate evidence of carcinogenicity, and evidence suggesting lack of carcinogenicity (IARC 2006, pp. 19-20). The IARC Working Group's finding that the epidemiology on glyphosate and NHL provides "limited evidence of carcinogenicity" (IARC 2015, p. 78) – defined as "A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence" – best fits the evidence.

2.0 ANALYSIS AND INTERPRETATION OF ANIMAL DATA

2.1 Dose selection

EPA misrepresents its own test guidelines when it states that: "the high dose ***is not recommended to exceed*** 1,000 mg/kg/day (OCSPP 870.4200; OCSPP 870.4300)" (EPA 2016, p. 71, emphasis added). The actual words are "***need not exceed***," which is very different. EPA's inaccurate wording gives the false impression that the guidelines recommend ***a cap*** on the highest dose, when in fact they establish ***a floor*** in certain cases.

The guidelines EPA cites are for the conduct of carcinogenicity (OCSPP 870.4200) and combined chronic/carcinogenicity (OCSPP 870.4300) studies. They have identical language on high dose selection. The highest dose tested:

1) "should elicit signs of toxicity without substantially altering the normal life span due to effects other than tumors;" ***but***
2) "***need not*** exceed 1,000 mg/kg/day." (EPA 1998a, 1998b, emphasis added)

Thus, dose levels that satisfy clause 1) above are acceptable, even if they exceed 1,000 mg/kg/day. The high dose is not defined by some arbitrary number, but rather by the biological

effects of the test compound on the test animal. It should be high enough to be toxic, but not so high as to affect survival due to effects other than tumors. Clause 2) is secondary, and merely allows the performing lab to utilize a highest dose ***as low as*** 1,000 mg/kg/day when doses in excess of this level are found ***not*** to elicit the signs of toxicity demanded in 1). Hence, 1,000 mg/kg/day serves as the minimum high-dose level in these cases.

This same mischaracterization of 1,000 mg/kg/day as the maximum dosage is evident when EPA states that "[a] large number of the carcinogenicity studies conducted with glyphosate approach or exceed ***the limit dose"*** (EPA 2016, p. 71, emphasis added). The only limit mentioned in EPA Guidelines is a practical one: "5% of the test substance in the feed for dietary studies" (EPA 2005, 2-17). None of the evaluated studies administer glyphosate at this high level. EPA's mischaracterization of its test guidelines leads it to incorrectly discount tumor findings at doses ≥ 1,000 mg/kg/day.

2.2 Interpretation of high-dose findings

EPA attempts to justify its discounting of tumor findings in high-dose groups by reference to EPA (2005), but once again inappropriately:

> The 2005 EPA Guidelines for Carcinogen Risk Assessment state that "weighing of the evidence includes addressing not only the likelihood of human carcinogenic effects of the agent but also the conditions under which such effects may be expressed." As such, the agency puts less weight on observations of tumors that occur near or above the limit dose (EPA 2016, p. 71).

EPA's faulty premise here appears to be that tumors occurring in animals exposed to the "limit dose" of 1,000 mg/kg/day may be safely discounted because this dose far exceeds human exposure levels (EPA 2016, p. 96). This is a basic misunderstanding. First, as EPA states elsewhere in its guidelines: "The high dose in long-term studies is generally selected to provide the maximum ability to detect treatment-related carcinogenic effects…" (EPA 2005, 2-15). According to an OECD guidance: "[t]he top dose is chosen to increase the study's statistical power to detect effects that may be rare" (OECD 2012, p. 57). None of this is controversial; it is long-standing, well-accepted practice in toxicology that the high dose should be at or near the animal's maximally tolerated dose, without regard to anticipated human exposure levels.

Second, if one were to accept EPA's premise, one would also have to discount many tumor findings in lower dosage groups, since in most studies they too exceed anticipated human exposure levels. Yet EPA Guidelines make clear that even "[t]he middle and lowest doses should be selected to characterize the shape of the dose-response curve as much as possible," not to mimic human exposure levels (EPA 2005, p. 2-18).

Third, EPA has once again mischaracterized its own guidance document. The passage EPA quotes above does ***not*** refer to the procedure for interpreting individual animal studies. Rather, it appears in a section describing the ***overall hazard*** assessment that occurs only ***after*** all the human, animal and other evidence has been collected and weighed separately:

> "The cancer guidelines emphasize the importance of weighing ***all*** of the evidence in ***reaching conclusions*** about the human carcinogenic potential of agents …. ***in a single integrative step after assessing all of the individual lines of evidence***…" (EPA 2005, Section 1.3.3: Weight of Evidence Narrative, emphasis added).

In other words, the neoplastic findings of properly conducted animal studies, in all dosage groups, must be objectively interpreted on their own terms, according to accepted standards for animal toxicology studies. The weighing of their human significance comes only later, in the context of the overall hazard assessment. Thus, EPA should in no way discount or give lesser consideration to tumors that occur in animals treated with high doses of glyphosate based on considerations of human exposure, because such considerations are entirely inappropriate at this stage of the assessment process.

2.3 Statistical evaluation

Consistent with its 2005 Guidelines, EPA employs the Cochran-Armitage trend test and the Fisher Exact test to statistically assess tumor incidence trends and differences in incidence between treatment and control groups, respectively. "Significance [at $p < 0.05$] in either kind of test is sufficient to reject the hypothesis that chance accounts for the result" (EPA 2016, p. 72; EPA 2005, 2-19).

In this glyphosate assessment, however, EPA departs from its Guidelines by demanding that "the data demonstrate a monotonic dose-response" (EPA 2016, p. 72). As discussed below, EPA repeatedly discounts statistically significant trends and/or pairwise comparison findings largely because the incidence rates do not perfectly fit a monotonic dose-response pattern:

$$\text{Control \%} < \text{Low-dose \%} < \text{Mid-dose \%} < \text{High-dose \%}$$

CFS has found no support for this inappropriate, excessively demanding criterion of biological significance in the 2005 Guidelines for Carcinogen Risk Assessment (a search of that document turned up zero hits for the term "monotonic"), or in any similar guidance document. The illegitimacy of this criterion is underscored by EPA's language.

> "If a trend was found to be statistically significant, ***a closer examination of the tumor incidence*** was taken to determine whether the data demonstrate a monotonic dose-response where an increase in tumor incidence is expected with corresponding increase in dose." (EPA 2016, p. 72, emphasis added)

EPA has it backwards. Whether or not tumor incidence data fit a monotonic pattern is easily discernable from visual inspection of the data (and simple long division). It is the statistical analysis of such data that constitutes the "closer examination" that is required to discern trends with potential biological significance. To state the obvious: Practical limitations on treatment group size mean that innate biological variability among individuals in susceptibility to the test agent (among other factors) make it unlikely that all but potent carcinogens will elicit tumor

incidence findings that perfectly fit a monotonic dose-response pattern. This is why statistics are applied in the first place – to discern trends amidst the unavoidable biological background "noise" when statistical power is low. The Panel should disregard EPA's demand for monotonic dose-response as the standard for biological significance of tumor findings.

2.4 Use of historical control data

Data on spontaneous lesions in control animals from other experiments can be useful in contextualizing findings. As EPA explains in its 2005 Guidelines (Section 2.2.2.1.3), such data may "reinforce or weaken the significance given to the response" in the current study. In the case of uncommon tumors, historical control data may support the biological significance of increased tumor incidence in a treated group even when it is not statistically significant in comparison with concurrent controls (Id.). In the case of common tumor types, "statistically significant increases in tumors should not be discounted simply because incidence rates in the treated groups are within the range of historical controls or because incidence rates in the concurrent controls are somewhat lower than average" (Id.).

Despite these guidelines, in the glyphosate assessment EPA consistently uses historical control data in only one direction: to discount the biological significance of increased tumor incidence in treatment groups. Conversely, EPA sometimes fails to consult historical controls in cases where they would support biological significance. We discuss examples below in comments on the individual studies.

The purpose of historical control data is to provide a more accurate estimate of the spontaneous rate of a given lesion in a particular strain of animal than can be had from the concurrent control. Because they have more statistical power, larger historical control datasets are preferable to smaller ones, all other things being equal.[3] For the same reason, comparisons should be limited to the ***mean*** incidence of the relevant lesion in the ***pooled dataset***, rather than to the "range of historical controls" based on incidences in separate groups. This is because each individual group in the historical control "pool" suffers from the same lack of statistical power as the concurrent control (assuming they are similarly sized). The upper- and lower-bound group incidences that bracket the range are unrepresentative of the lesion's spontaneous prevalence, which is best indicated by the mean. The upper bound of the historical control range, in particular, can be illegitimately used to discount significant findings in the current treatment group(s).

[3] Spontaneous tumor prevalence is of course also a function of factors beyond the strain's genetics, such as laboratory-specific rearing practices and pathological examination methods. Obtaining historical control data from animals reared in the same lab in the same time period as the concurrent study can help control for these factors. Other historical control data may also be used, but only with caution (EPA 2005, 2-21).

3.0 RAT STUDIES

3.1 Burnett et al. 1979

EPA erroneously presents this study as one involving oral administration of "glyphosate (as an aqueous monosodium salt solution)" to albino rats (EPA 2016, p. 74). In fact, the title of this study shows that the rats were fed a compound designated CP-76100, which is a glyphosate ***contaminant,*** N-nitrosoglyphosate, not glyphosate.

> Burnett, P., Borders, J.; Kush, J. (1979). Report to Monsanto Company: Two Year Chronic Oral Toxicity Study with CP-76100 in Albino Rats: IBT No. 8560-08924. (Unpublished study received Jun 24, 1982 under 524-308; prepared by Industrial Bio-Test Laboratories, Inc., submitted by Monsanto Co., Washington, DC; CDL:247746-A; 247745; 247747; 247748; 247749; 247750; 247751; 247752) (EPA 2016, p. 145)

The fact that CP-76100 is N-nitrosoglyphosate is documented by two EPA memos from the 1980s. The first is an EPA review of a different study on "the oral toxicity of CP76100 (sodium salt of N-nitrosoglyphosate), an impurity in Roundup herbicide" to hamsters (EPA 1/10/83). The second reviews a "two-year oral toxicity study with CP 76100 in albino rats" and likewise identifies the chemical being tested as "N-nitrosoglyphosate (sodium salt), CP 76100; 19.8% a.i." (EPA 6/25/85). Thus, this study has been erroneously presented as a study on glyphosate, and cannot serve as a test of glyphosate's carcinogenic potential.

In addition, this second EPA memo (6/25/85) appears to be a review of the Burnett et al., 1979 study at issue here.[4] If this is so, the study is invalid even as a carcinogenicity test of the contaminant, N-nitroso-glyphosate. The EPA reviewer ruled the study invalid due to excessive mortality in control rats, which he attributed to errors in the calculation of the salt content in control group saline solutions. Control rats received four times the amount of sodium as the high-dose group: "The amount of salt given controls appears to have had a toxic effect …. The study is therefore compromised due to the lack of an adequate control group, and is considered to be invalid" (EPA 6/25/85). That the study reviewed in EPA (6/25/85) is in fact Burnett et al, 1979, despite the discrepancy in authors (see previous footnote), is also supported by EPA's description of it in the Issue Paper: "A higher mortality rate was noted in the control group in comparison to the treated groups after 12 and 24 months of testing" (EPA 2016, p. 74).

In the 1970s and 1980s, EPA required carcinogenicity tests on nitroso contaminants in pesticides when their levels exceeded 1.0 ppm. In 1991, EPA concluded that N-nitrosoglyphosate (NNG) was no longer of toxicological concern because 92.6% of tests on technical glyphosate samples contained less than 1.0 ppm NNG (EPA 10/30/91, p. 16).

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[4] The cited memo (EPA 6/25/85) reviews a study with the same title, report number (IBT 8560-08924), date submitted (6/24/82) and accession/CDL numbers as the study at issue here, but with different authors listed (Morrow, LD et al. rather than Burnett et al.). The memo also lists the "report date" as 5/14/79, which matches the date reported for this study in the title it is given in the SAP docket: "Two year chronic oral toxicity with CP-76100 in albino rats Burnett et al. 05/14/1979." EPA-HQ-OPP-2016-0385-0021.

It is not surprising that this study was flawed. The firm that conducted it, Industrial Bio-Test Laboratories (IBT), ran a notoriously shoddy and corrupt operation, and falsified a huge number of studies on pesticides and other compounds that it conducted on contract with Monsanto and other companies in the 1970s (Schneider 1983). After a seven-year review of many hundreds of IBT studies in its files, EPA found in 1983 that less than 10% were scientifically valid. In 1983, a federal court convicted four IBT officers of fraud and falsifying statements and scientific data submitted to the government. One of the four, toxicologist Paul Wright, had left Monsanto to join IBT in 1971, where he worked for 18 months, falsifying data on IBT studies of at least one Monsanto compound, before returning to Monsanto. The episode is widely regarded as one of the most massive scientific scandals in American history (Schneider 1983).

It is not clear how this study passed EPA's study quality review process (EPA 2016, p. 69 ff). CFS recommends that the Panel ignore this study in its assessment.

3.2 Lankas, 1981

Testicular interstitial cell tumors

In this 2-year study in Sprague-Dawley rats conducted by Bio/dynamics, EPA reports a significant trend of testicular interstitial cell tumors in males, with pairwise comparison significant even after multiple comparisons adjustment (0.039). It appears that EPA misreported the high-dose incidence rate in Table 4.1 (6/44 = 14%, not 12%).

EPA concludes that the tumors are not treatment-related for three major reasons: lack of monotonic dose response; "unusually low" incidence in the concurrent control (0/50) relative to historical control data; and incidences in the glyphosate-treated groups that were "within the normal biological variation for this tumor type in this strain of rat."

Monotonic dose-response is not a valid criterion. With a historical control mean of 4.5%, the concurrent control incidence is not "unusually low," and EPA Guidelines warn against dismissal when concurrent control incidence is only "somewhat lower than average," the case here. Finally, these results are not within "normal biological variation." Charles River (2004) reports a 2.65% incidence of testicular interstitial cell tumors in a large control database of Sprague-Dawley rats (57/2145). High-dose (14%) and even low-dose (6.4%) incidences exceed the historical control data.

Although this finding was not replicated in other reviewed studies, the strong statistical significance argues against dismissal.

Lymphocytic hyperplasia of the thymus in females

An early EPA review of this study (EPA 2/9/82, pp. 3-5) found statistically significant increases in lymphocytic hyperplasia of the thymus in mid- and high-dose female rats, with a nearly significant elevation in the low-dose group as well (see following table). Roughly 40% of low-dose rats and 50% of mid- and high-dose animals exhibited hyperplasia, despite the low doses administered in this study. EPA (2016) does not discuss these findings, even though hyperplasia

can be a preneoplastic alteration, and thymus tumors (lymphoma + thymoma) are quite uncommon (0.49%) in female SD rats (Charles River 2004).

Test for Significance of Differences Between Proportions 2/5/82

Lymphocytic hyperplaasia

ppm	# RESP	Total	%	+/-2(S.D.)	One Tail P Statistic Fisher's
0.000	5	25	20.00	+/-(17.68)	
30.000	13	32	40.63	+/-(18.58)	0.084
100.000	18	37	48.65	+/-(17.46)	0.020
300.000	17	34	50.00	+/-(18.28)	0.017

Test for a linear trend is not significant

Source: EPA (2/9/82). Discussion in text specifies "lymphocytic hyperplasia of the thymus"

3.3 Stout and Ruecker, 1990

In this 2-year study in Sprague-Dawley rats conducted by Monsanto, EPA improperly discounted tumor findings in the high-dose groups (940/1183 mg/kg/day, M/F) based on the false premise of an excessive dose, as discussed in 2.1 above. There were no significant increases in mortality, and no evidence a maximum tolerated dose was exceeded.

EPA fails to report that 10 of 60 animals per sex per dose were sacrificed after 12 months (Greim et al. 2015, p. 191). There are unexplained discrepancies in the tumor data. The pancreatic and hepatocellular tumors in males were apparently identified from among the 50 animals per dose assigned to the 24-month groups, while thyroid C-cell tumors were reported from among the larger groups of 60 (male and female) that included animals sacrificed at 12 months. In addition, based on the data in EPA's tables and the corresponding raw data in Greim et al. (Supplemental, Study 2), it appears that a number of animals assigned to the 24-month treatment groups (those that died early) were not examined for pancreatic or hepatocellular tumors. For instance, only 28 of 31 low-dose males and 32 of 33 high-dose males that died early were examined for pancreatic islet cell tumors. It is also not clear why EPA excluded from certain control group counts animals "that died or were sacrificed prior to study week 55" (footnotes "a" to Tables 4.2, 4.4, 4.6 and 4.7). The discussion below is based on the numbers as reported in EPA (2016).

<u>Pancreatic islet cell tumors in males</u>

There are significant differences in the incidence of these tumors in the low-dose and high-dose treatment groups for adenomas (raw p-value) and still marginal significance for the Sidak-adjusted low-dose group (0.052) versus the concurrent control. EPA dismisses these findings based on unusually low incidence in the concurrent control, even though 1/43 = 2.3% is not unusual; it is above the low-end historical group incidence of 1.8%. More importantly, Table 4.2 shows that the incidences of adenomas as well as adenomas/carcinomas are two to over three times the mean incidence rate of Monsanto's pooled historical controls ***in all treatment groups***, with still higher multiples versus the concurrent control.

Hepatocellular tumors in males

There is a significant trend of increasing adenomas (P = 0.022) and a marginally significant trend in adenomas/carcinomas (P = 0.078). EPA states that no hyperplasia was observed except in a single mid-dose animal, but in fact a second animal (in the high-dose group) also exhibited hyperplasia (EPA 6/3/91, pdf p. 19). No historical control data is presented, but Charles River (2004) reports a mean combined incidence of hepatocellular adenomas + carcinomas in SD control rats of just 4.2%, well below the incidences in all treatment groups of this study.

Thyroid C-cell carcinomas

Significant trends were observed for both adenomas and adenomas/carcinomas in females, which according to EPA's 2005 guidelines is sufficient to rule out chance as responsible for the result, even with lack of significance in pairwise comparison. There was also a considerable incidence of hyperplasia, which was dismissed on the illegitimate grounds that it did not fit a perfect monotonic dose-response pattern. These results in females are supported by the marginally significant trends in males for incidence of both adenomas (0.079) and combined adenomas/carcinomas (0.087), as well as the presence of hyperplasia.

3.4 Atkinson et al., 1993a

EPA (2016) gives too little data on this study for evaluation by the SAP, stating only that "[t]here were no treatment-related increases in tumor incidences in the study." However, the study is reported in more detail in a supplemental EPA memorandum posted to the SAP docket that is entitled: "Glyphosate: Review and generation of Data Evaluation Records for three rodent carcinogenicity studies" (see EPA-HQ-OPP-2016-0835-0091, pp. 20-22).

There was a high incidence of tumors in all groups: 44/50 in control males; 41/50 in high-dose males; 49/50 in control and high-dose females. However, the number of males with malignant tumors in the high-dose group (15/50 = 30%) was double that observed in controls (8/50 = 16%). The number of total malignant tumors in females was similar in the control (38%) and high-dose (32%) groups. While all groups had neoplastic lesions, the memorandum does not provide any data on tumors in low- or mid-dose animals, male or female.

Two of 43 males in treatment groups (dosage group or groups not specified) had prostate tumors (one carcinoma and one adenoma), while neither adenomas nor carcinomas were observed in controls (0/42). Haemangiosarcoma was identified in the spleen of 1/49 males in the high-dose group, 0/50 in controls. The memo states that: "Haemangiosarcoma was also present in the vascular system of 1/1 male at the high dose (0/1 in control)." Does this mean that only 1 animal of each group was examined?

The performing lab did not provide historical control data. However, data from Charles River (2004) shows that these are all quite rare tumors in male Sprague-Dawley rats. Among control rats from 30 studies, only 6 prostate adenomas (no carcinomas) were reported (2144 prostates examined), for an incidence of 0.28%. Haemangiosarcoma in the spleen is even rarer: 1/2144 =

0.05% among males and 1/2344 = 0.04% in females. Haemangiosarcoma incidence in whole body/multiple organs is likewise rare: 2/2146 = 0.09% in males and 2/2344 = 0.09% in females.

In light of the high incidence of total tumors, malignant tumors, and the two-fold higher incidence of malignancies in high-dose versus control males, there should be fuller reporting of tumors by tissue for review by the SAP. Although few prostate adenomas and haemangiosarcomas were found, they were all found in treatment groups, and may be compound-related in light of their rarity in Sprague-Dawley rats.

3.5 Brammer, 2001

In this 24-month study, there was a highly significant trend of increased liver adenomas (P = 0.008) in male Wistar rats (0/52, 2/52, 0/52, 5/52 from control to high-dose), and a marginally significant difference in the pairwise comparison of high-dose to control after multiple comparisons adjustment (P = 0.056). EPA does not report historical control data, but liver tumors appear to be uncommon in Wistar rats. Bomhard (1992) reports a mean frequency of 1.9% for spontaneous liver tumors in Wistar rats in 30-month studies (9 control groups from 7 studies). The incidence at month 24, the length of this study, is likely still lower. High-dose males had higher survival and a 5% reduction in body weight versus controls, so the high dose was not excessive. EPA dismisses the results mainly because of non-monotonic dose-response and a supposedly excessive high dose.

There is a slight discrepancy in reporting of inter-current or early (E) and terminal (T) deaths in three of four groups that should be clarified. E+T deaths for the control (37+16), low-dose (36+17) and mid-dose (35+18) groups add up to 53, though each group had only 52 rats. The same discrepancies are found in Greim et al. (2015)'s account of this study (Table 12).

3.6 Pavkov and Wyand, 1987

This study involved a high-dose of just 41.8/55.7 mg/kg/day (M/F) of sulfosate (glyphosate-trimesium), and EPA provides no evidence that it even approached a maximally tolerated dose. Therefore, this study does not provide a sufficiently stringent test of potential carcinogenicity.

This study should also be rejected because sulfosate has different toxicological properties than other salts of glyphosate, and so may not be comparable in terms of carcinogenic potential. Sulfosate (aka glyphosate-trimesium) is the trimethylsulfonium salt of glyphosate. EPA has always regulated it is an active ingredient distinct from glyphosate acid and all other salts (e.g. isopropylamine, sodium, potassium), which are treated collectively as "glyphosate." For instance, EPA required submission of an entirely separate suite of toxicology (including carcinogenicity) studies on sulfosate, distinct from those collected for glyphosate (EPA 9/11/98, see especially 48600-48602). This study has never before been used to support registration of glyphosate. EPA also issued separate food tolerances for sulfosate, distinct from those issued for glyphosate (EPA 9/11/98). EPA even declined to make a finding that sulfosate and glyphosate share a common mechanism of toxicity, stating that: "[s]ulfosate is structurally similar to glyphosate" but that "EPA does not have … available data to determine whether sulfosate has a common mechanism of toxicity with other substances…" (e.g. glyphosate) (EPA 9/11/98:

48603).[5] Sulfosate exhibits a different toxicological profile than other salts of glyphosate with respect to acute toxicity (Sorensen and Gregersen 1999) and neurotoxicity (EPA 9/11/98: 48604). Finally, EPA set different chronic oral reference doses[6] for sulfosate and glyphosate, based on the different findings in their separate suites of toxicology studies. EPA cancelled the last registrations for sulfosate in 2004, and food tolerances in 2007 (EPA 5/2/07), so the herbicide has not been used in the U.S. for nearly a decade.

3.7 Suresh, 1996

EPA reports no adverse effects on survival and no signs of toxicity, suggesting that the high dose was not high enough to provide a sufficiently stringent test of glyphosate's carcinogenicity, according to EPA guidelines. Greim et al. (2015) agree. Their report on this study (they refer to it as Feinchemie Schwebda 1996) states: "There were no treatment-related deaths or clinical signs in any of the dose-groups. Moreover, there were no treatment-related effects on body weight gain or food consumption noted**.** This suggests that the MTD may not have been reached by the applied dosing regimen."

3.8 Enemoto, 1997

This was a two-year study in Sprague-Dawley rats, reported more fully in Greim et al. (2015) under the name Study 6 (Arysta Life Sciences 1997b). Decreased body weight, increased cecum weight, distension of the cecum and loose stool in the high-dose groups suggested that the maximum tolerated dose (MTD) was achieved. EPA reports no changes in mortality at any dose, so the MTD was not exceeded, and the high dose was below the upper limit of 5% of feed specified in EPA (2005). EPA reports no treatment-related increases in tumors, but apparently on the the sole grounds that pairwise comparisons were not significant in the Fisher exact test,[7] without testing for significant trends. However, Greim et al (2015) and the supplementary data for that paper suggest a possible treatment-related increase in lung tumors in male rats (see table below). The combined incidence for lung tumors was: 0/50, 3/50, 2/50 and 4/50. No historical control data are reported for this study. Charles River (2004) data suggests that lung adenomas and adenocarcinomas are quite rare in male Sprague-Dawley rats (combined incidence: 5/2146 = 0.23%).

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[5] Since the passage of the Food Quality Protection Act in 1996, EPA has been required to assess the cumulative effects of pesticides that the Agency determines share a common mechanism of toxicity, e.g. organophosphate insecticides. See https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/cumulative-assessment-risk-pesticides.

[6] The chronic oral reference dose (cRfD) is the maximum daily level of exposure to a pesticide that EPA regards as safe over a lifetime (expressed in mg/kg bw/day).

[7] See SAP docket entry entitled: "Glyphosate. Completion and submission of toxicology data evaluation records" (Docket No. EPA-HQ-OPP-2016-0385-0097), pdf p. 8.

Lung Tumors in Enemoto, 1997					
	Dosage (ppm)				Source: Greim et al. (2015), Study 6
MALE Sprague-Dawley Rats	**0**	**3000**	**10000**	**30000**	**Source**
Lung adenoma – terminal	0/18	2/20	1/18	3/29	Greim et al. (2015), Table 11
Lung adenoma - dead/moribund	0/32	1/30	0/32	0/21	Greim et al. (2015), Supplemental, Table 25-10
Lung adenocarcinoma - dead/moribund	0/32	0/30	0/32	1/21	Greim et al. (2015), Supplemental, Table 25-10
Lung squamous cell carcinoma - terminal	0/18	0/20	1/18	0/29	Greim et al. (2015), Supplemental, Table 25-7
Totals for Lung Tumors	**0/50**	**3/50**	**2/50**	**4/50**	
Incidence	**0%**	**6%**	**4%`**	**8%**	

Sources: Greim et al. (2015), Table 11, reports lung adenoma – terminal; for other data, see Greim et al. (2015 Supplemental, Study 6).

3.9 Wood et al, 2009a

In this two-year Wistar rat study, a highly significant trend in combined incidence of mammary adenomas and adenocarcinomas was identified (4%, 6%, 2%, 16%, P = 0.008). There was also a significant pairwise difference between high-dose and control (P = 0.046) which became less significant with multiple comparisons adjustment (0.132). No dosage effects on survival were noted, so a maximum tolerated dose was not exceeded.

3.10 Review of rat studies

Two of the nine rat studies should be rejected without evaluation, for the reasons discussed above under 3.1: Burnett et al. 1979 and 3.6: Wyand and Pavkov. Of the remaining seven, four (see 3.2, 3.3, 3.5, 3.9) and possibly five (3.8) provide significant evidence of compound-related tumors. A significantly higher incidence of liver tumors were reported in two studies in two strains of rat (Stout and Ruecker 1990, Brammer 2001). Suresh, 1996 (3.7) did not achieve an MTD, and so did not meet EPA guidelines for high-dose selection. Fuller reporting of Atkinson et al. 1993a (3.4) for the SAP's review is needed given the high incidence of tumors and presence of rare tumors. EPA's dismissal of high-dose results in illegitimate.

4.0 MOUSE STUDIES

4.1 Reyna and Gordon, 1973

The SAP should exclude this study from its evaluation for several reasons. First, it fails in several respects to meet EPA test guidelines for animal carcinogenicity studies (EPA 1998a):

1) Only two dosage groups were used, whereas test guidelines demand "at least three dose levels … in addition to the concurrent control group" (p. 3)

2) Only 10 of 50 mice/sex/dose were examined for histopathological changes, whereas test guidelines specify: "Full histopathology on the organs and tissues listed under paragraph (d)(9)(iii) of this guideline ***of all animals in the control and high-dose groups*** and all animals that died or were killed during the study" (p. 10, emphasis added).
3) EPA's 2016 review of this study determined that it was "non-guideline" for the reasons given above, and because "the study did not test up to the recommended limit dose."[8] 17 and 50 mg/kg/day are extremely low doses, and there were no signs of toxicity or effects of dose on survival.

EPA (2016) states: "Although only ten mice/sex/dose were examined for histopathological changes, there were no statistically significant increases in tumors observed in the study; therefore, this deficiency would not impact the overall conclusion regarding tumor findings." (p. 85). On the contrary, the "overall conclusion regarding tumor findings" could obviously have been quite different if examination of the 80% of mice (40 of 50) per group that were not examined turned up statistically significant incidences of tumors in treatment groups. Ten mice provide too little statistical power to make any valid conclusions.

Finally, there is a question as to the validity of this study. The citation (reproduced below) identifies it as IBT No. B569, conducted in 1973 and validated by the sponsor (Monsanto) in 1978.

> Reyna, M.S. Gordon, D.E. (1973) 18-Month Carcinogenic Study with CP67573 in Swiss White Mice: IBT No. B569. (Unpublished study, including sponsor's validation report dated Feb 1, 1978, received Jun 21, 1978 under 524-308; prepared by Industrial Bio-Test Laboratories, Inc., submitted by Monsanto Co., Washington, D.C.; CDL:234136-G). MRID 00061113. Unpublished.

As explained in Section 3.1 above, the performing lab, Industrial Bio-Test Laboratories (IBT), submitted to EPA many hundreds of pesticide studies that contained falsified / fabricated data, or were otherwise inadequate, in the 1970s (Schneider 1983). This forced EPA to conduct a lengthy review. In 1983, EPA published a list of IBT studies that had been reviewed and their status. A study designated IBT No. B569 (the same as this study) was ruled "invalid" as follows:

IBT_NUM	CHEMICAL	COMPANY	ROUTE	TYPE	SPECIES	VALIDATE	EVALUATE	REPLACE
B-569	GLYPHOSATE	MONSANTO		CARCINOGENICITY	MOUSE	I	NA	REPLACED

Source: EPA (1983). "Summary of IBT Review Program," Office of Pesticide Programs, July 1983. Excerpted from pdf p. 37.

Under "Validate," "I" indicates a study that is "Invalid: The information in the final report was not supported by the raw data from the study." This EPA review was published ten years after

[8] See SAP docket entry entitled "Glyphosate. Completion and submission of toxicology a [sic] data evaluation record." Sept. 9, 2016. Docket No. EPA-HQ-OPP-2016-0385-0096, p. 4.

the study date, and five years after the the date of the sponsor's validation report. The entry also indicates the study was "replaced," but it seems unlikely that a valid replacement study would bear the same IBT No. B569 as the invalidated one.

4.2 Knezevich and Hogan, 1983

In this study, glyphosate was administered to CD-1 mice for nearly two years at 1,000, 5,000 and 30,000 ppm (Greim et al 2015, p. 198), with a significantly increased incidence of renal cell tumors identified. Below we address four major issues: 1) Interpretation of morphological alteration in one control mouse kidney; 2) Dosage considerations; 3) Historical control data; and 4) Procedural issues.

4.2.1 Interpretation of morphological alteration in one control mouse kidney

This mouse study was conducted by Knezevich and Hogan with the testing firm Bio/Dynamic, Inc., under contract with Monsanto. In male mice, Bio/Dynamic reported no renal tubule adenomas in either the control (0/49) or low-dose (0/49) groups, but one in the mid-dose (1/50) and three in the high-dose group (3/50). Based on an initial review of the study, EPA toxicologists found that "glyphosate is oncogenic, producing renal tubule adenomas, a rare tumor, in a dose-related manner" (EPA 2/10/84). Over a year later, a panel of eight EPA Toxicology Branch scientists conducted a second review of the study. After considering Monsanto's input, they issued a "Consensus Review of Glyphosate" in which they classified glyphosate as a Category 3 (possible) carcinogen (EPA 3/4/85). Monsanto engaged a consulting pathologist to re-examine the kidney sections. According to EPA's pathologist, Dr. Louis Kasza, D.V.M., Ph.D., the consultant characterized a "small localized change in one kidney of the control group" as a renal tubule adenoma. Dr. Kasza disagreed, describing the change as a small "morphological alteration" that "does not represent a pathophysiologically significant change" (EPA 12/4/85). Three additional renal sections were examined from each male kidney. No lesion was found in the additional sections from the suspect control mouse kidney (EPA 12/4/85). Examination of the additional sections from treatment group kidneys led to diagnosis of one and two carcinomas in the mid- and high-dose groups, respectively, whereas all original findings were adenomas (EPA 2016, Table 4.12).

The findings from additional kidney sections supported the original assessments by Bio/Dynamic and EPA's Toxicology Branch of no control mouse renal adenomas. Greim et al. 2015 (p. 199), whose authors include a Monsanto employee, also report that a renal tubule adenoma was "not seen in the concurrent control group," and their supplemental data (Study 10, p. 8) also support the original findings – 0/49, 0/49, 1/50, 3/50 – which yield a highly statistically significant trend of P = 0.016 (IARC 2015, p. 31). Even if one accepts the diagnosis of a renal adenoma in one control mouse, the trend is still significant (IARC) or at least marginally significant (EPA). IARC finds statistically significant trends for carcinomas alone (P = 0.037) and for adenoma/carcinoma combined (P = 0.034) (IARC 2015, p. 33). EPA finds marginal significance for the same (P = 0.063 and 0.065, respectively).

4.2.2 Historical control data

EPA cites an unidentified Pathology Working Group (PWG) (discussed further below) as dismissing the significance of the renal tumors in part because: "renal tubular cell tumors are spontaneous lesions for which there is a paucity of historical control data for this mouse stock" (EPA 2016, p. 86). In fact, by this time EPA had already collected considerable historical control data on renal tubule neoplasms in CD-1 mice. The mean incidence in male controls of the same strain, from the same lab (Bio/Dynamic) during the same time period (1978-1982) was 0.23% (3/1286) (EPA 10/31/91, p. 13). The spontaneous incidence rates of renal cell tumors in male CD-1 mice are reasonably consistent across labs and time periods. For instance, Chandra and Frith (1994) report a corresponding incidence rate of 0.14% (1 of 725) in male CD-1 mice.

The 2% (1/50) and 6% (3/50) incidences in the mid- and high-dose groups far exceed the low spontaneous rates of these neoplasms found in male controls from the same lab and time period, as well as in other data for this strain. EPA's 2005 Guidelines state that:

> "In analyzing the results for uncommon tumors in a treated group that are not statistically significant in comparison with concurrent controls, the analyst may be informed by the experience of historical controls to conclude that the result is in fact unlikely to be due to chance." (EPA 2005, pp. 2-20 to 2-21).

The weight-of-the-evidence, including a proper weighing of the rarity of this tumor in male CD-1 mice, supports the conclusion that the renal tubule tumors are compound-related.

4.2.3 Dosage considerations

EPA (2016) discounted the tumor findings in the high-dose and mid-dose groups based on the false premise of excessive dose (see Sections 2.1 and 2.2 above), when in fact 30,000 ppm (3% of feed) is below the 5% limit cited in EPA Guidelines for dietary studies. In this study, "[n]o treatment-related toxic signs were noted during the study," demonstrating that the high dose was not excessive (EPA 4/3/85). EPA (2016) states that "[n]o effect on survival was observed" at any dose. Thus, EPA improperly discounted tumor findings in the high-dose and mid-dose groups.

EPA reports all doses differently (higher) than Greim et al. (2015), for instance for the high-dose group 4945/6069 versus 4841/5874 mg/kg/day (M/F). Greim et al. (p. 198) also note that this 24-month study involved administration of glyphosate "over a period of ***nearly*** two years" and cite conflicting figures for dosage of the high-dose group: 10,000 ppm and 30,000 ppm (Table 15 vs. p. 198). These discrepancies should be clarified.

4.2.4 Procedural issues

Monsanto exercised considerable and in some respects undue influence on many aspects of this study. It was conducted by a testing firm contracted by Monsanto. The company engaged a pathologist to dispute the initial interpretation of tumor findings by Bio/Dynamic and EPA pathologists. Monsanto also decisively influenced EPA's use and interpretation of historical control group data. EPA initially insisted on using the mean incidence rate of renal tumors of

pooled control groups as the proper standard of comparison (EPA 2/26/85), which as argued above is the proper approach. Monsanto successfully persuaded the Agency to utilize instead the unrepresentative, upper bound of "historical ranges" of tumor incidences in individual control groups in an effort to minimize the significance of treatment group tumor findings, and to argue against EPA's initial demand that the mouse study be repeated (EPA 6/19/89). To our knowledge, the mouse study was never repeated. We know little about the Pathology Working Group (PWG) referred to above. EPA says that it requested a PWG to evaluate the kidney sections (EPA 2016, p. 85), but we do not know who selected the PWG members; or what relationship, financial or otherwise, existed between them and Monsanto. However, we do know that the five members of the PWG reported directly to Monsanto (EPA 3/11/86, p. 7, see "Letter of October 10, 1985, from Pathology Working Group (PWG) to Monsanto").

EPA's description of the history of this disputed study downplays the dissenting views of its own scientists. In addition to the points raised above, as late as 1991 three EPA scientists on an internal peer review committee did not concur with the conclusion that glyphosate is not carcinogenic (EPA 10/31/91).

4.3 Atkinson et al. 1993b

Seven haemangiosarcomas were observed in four CD-1 mice of the high-dose male group (4/45 = 9%), none in the control or other two treatment groups. Based on number of animals (not tumors), the trend is highly significant (p = 0.003) and the pairwise comparison marginally significant (p = 0.053). EPA (2016) suggests that haemangiosarcomas are common in CD-1 mice, but presents no data in support of this contention. In fact, haemangiosarcomas are uncommon tumors in this strain. Historical control data from Charles Rivers (2000) shows incidence rates of haemangiosarcomas in male CD-1 mice as follows: liver (29/2571 = 1.1%), spleen (29/2543 = 1.1%), and prostate (none reported[9]), versus rates in this study of liver (3/45 = 7%), spleen (3/45 = 7%), and prostate (1/45 = 2%).

The presence of haemangiosarcomas in female as well as male mice, and multiple tumors in some mice, support a treatment-related effect (EPA 2005, 2-21 to 2-22). Although EPA (2016) does not present the female data, they are reported in a memo in the SAP docket.[10] Haemangiosarcomas were found in two female treatment groups (2/50 low-dose, 1/50 high-dose, with none in the control group) – one each in the liver (high), spleen (low) and uterus (low-dose). Though not statistically significant by either trend or pairwise comparison, spontaneous haemangiosarcomas are even rarer in female CD-1 mice: liver (17/2740 = 0.6%); spleen (12/2772 = 0.4%) and uterus (14/2812 = 0.5%) in data from Charles River (2000). Second, the lack of any treatment-related effect on body weight or survival in any of the dosed groups relative to controls (JMPR 2004, p. 122; IARC 2015, p. 33) suggests that the high dose was not

[9] Charles River reports findings for prostate tumors in 2565 control mice from 46 studies. One adenoma (0.04%) is the only lesion reported. Presumably, prostate haemangiosarcomas would have been reported if any had been identified.

[10] See SAP docket entry entitled: "Glyphosate; Review and generation of Data Evaluation Records for three rodent carcinogenicity studies." Docket No. EPA-HQ-OPP-2016-0385-0091.

excessive. The lack of a monotonic dose response dose is not sufficient to refute the biological significance of these findings. The weight of the evidence supports a treatment-related effect.

4.4 Wood et al., 2009b

In this 18-month CD-1 mouse study, there were no effects of dose on survival, and no evidence to suggest an MTD had been reached. Significant trends were identified for lung adenocarcinomas (P = 0.028) and malignant lymphomas (P = 0.007) in males with increasing dose. There was also a significant pairwise comparison (high-dose vs. control) for the lymphomas (P = 0.028), which remained marginally significant after multiple comparisons adjustment (P = 0.082).

Although the lymphomas exhibited both a significant trend ***and*** monotonic dose-response (0/51, 1/51, 2/51, 5/51), EPA dismisses their significance, despite its routine practice of dismissing significant trends because they are non-monotonic in other studies. EPA rejects the significant findings in the absence of historical control data from the performing lab, based primarily on such data from other labs, and these data appear to be misrepresented. The Giknis and Clifford (2005) control data cover 52 studies (not 59); 26 of the studies were for 2 years, yet EPA illegitimately included these studies for comparison to this 18-month study. EPA's range and mean also exclude studies where control groups had no lymphomas. When limited to the 18-month studies and with accounting of the 8 control groups with no lymphomas, the Giknas and Clifford historical control data yield a mean of just 2.7%. EPA provides no reference for the other control data, Son and Gopinath (2004). There is no reasonable or Guideline basis to deny the significance of these findings.

4.5 Sugimoto, 1997

In an 18-month study, CD-1 mice were fed glyphosate at doses ranging up to 40,000 ppm, below the 5% in feed limit specified in EPA Guidelines (2005) for dietary studies. There were no treatment-related effects on mortality or histopathological findings, so high-dose findings deserve full consideration. The mid-dose group received far less, 8,000 ppm, the low-dose 1600 ppm (Greim et al. 2015). There was a highly significant, monotonic dose-response trend in hemangiomas in female mice, which EPA dismisses despite a significant pairwise comparison between high-dose and control (raw p = 0.028) that remained marginally significant with multiple comparisons adjustment (p = 0.055). EPA reports no other treatment-related increases in tumors, but apparently on the the sole grounds that pairwise comparisons were not significant in the Fisher exact test,[11] without testing for significant trends. Thus, EPA failed to report significant trends in males of: 1) malignant lymphomas (4%, 4%, 0%, 12%, control to high-dose); 2) renal adenomas (0%, 0%, 0%, 4%); and 3) haemangiosarcomas (0%, 0%, 0%, 4%). (Greim et al. 2015, Table 17; Greim et al (2015 Supplement, Study 12, Table 20-5). Although the latter two are low response rates, the study was only18 months, and these tumors appeared in other studies.

[11] See SAP docket entry entitled: "Glyphosate. Completion and submission of toxicology data evaluation records" (Docket No. EPA-HQ-OPP-2016-0385-0097), pdf p. 8.

4.6 Pavkov and Turnier, 1987

This study should be rejected because sulfosate has different toxicological properties than other salts of glyphosate. Sulfosate was regulated by EPA as a different chemical than glyphosate, with an entirely different set of toxicology (including carcinogenicity) studies; different food tolerances; and different chronic oral reference doses. EPA declined to assign sulfosate and glyphosate a common mechanism of toxicity. Differences in the toxicological profiles of sulfosate and glyphosate include acute toxicity (Sorensen and Gregersen 1999) and neurotoxicity (EPA 9/11/98). Thus, sulfosate and glyphosate may also not be comparable in terms of carcinogenic potential. EPA has never used this study to support glyphosate registration. See Section 3.6 above for more detail.

4.7 Kumar, 2001

In this 18-month study in Swiss albino mice with a high dose of 10,000 ppm (= 1% of diet, well below the 5% limit dose), there were statistically significant trends in males for malignant lymphomas (20%, 30%, 32%, 38%) and renal cell adenomas (0%, 0%, 2%, 4%). (Greim et al. (2015) and Greim et al (2015 Supplement, Study 13).

EPA illegitimately excluded this study from the evaluation "due to the presence of a viral infection within the colony, which confounded the interpretation of study findings" (EPA 2016, p. 70). EPA presented no evidence of a viral infection, and this statement contradicts a fuller EPA review of this study in the SAP docket, where it is clear that this "viral infection" is purely a speculative inference from the presence of malignant lymphomas in all dose groups.

> "Murine leukemia viruses (MuLVs) are known to be a common cause of lymphoma in many different strains of mice (Ward 2006) [citation not provided] and ***may have potentially*** impacted this study. Taddesse-Heath et al. (2000) for example reported 50% lymphoma (mostly B-cell origin) incidence in a colony of Swiss mice infected with MuLVs. … A ***potential*** viral contamination of the colonies was noted and it's not clear how this impacted the study results." [12] (emphasis added)

EPA may have picked up the notion of a viral infection from industry reviewers Greim et al. (2015) (p. 201), who downgraded the study "based on speculation of a viral infection within the colony," and who, like EPA, cite Taddesse-Heath et al. (2000) in support.

Taddesse-Heath et al. (2000), however, do not provide much support for this weak speculation, and in fact present evidence against it.

> "Historically, Swiss Webster mice of the CFW subline, both inbred and random-bred stocks, have been considered to have a low spontaneous occurrence of

[12] See SAP docket entry entitled "Glyphosate. Completion and submission of toxicology data evaluation records" (Docket No. EPA-HQ-OPP-2016-0385-0085), pp. 9-10.

hematopoietic system tumors, and previous reports of infectious expression of murine leukemia viruses (MuLVs) have been rare and unremarkable."

Their findings of high lymphoma incidence are "in marked contrast" to this history, and are limited to their study, which involved "CFW mice from one source observed by two laboratories over a 2-year period … It should be noted that the several strains of outbred and inbred Swiss Webster mice designated as CFW in use in the United States and in Europe should not be considered to be identical."

EPA should have included this study in its review.

4.8 Review of mouse studies

EPA reviewed six studies. The Reyna and Gordon (1973) and Pavkov and Turnier (1987) studies should be excluded from the evaluation for the reasons discussed above under Sections 4.1, 4.6, and 3.6. Kumar (2001) should be included (Section 4.7). Of the five studies of this group, significant renal tumor findings were made in three (Knezevich and Hogan 1982, Sugimoto 1997 and Kumar 2001). Two studies (Atkinson et al. 1993b and Sugimoto 1997) showed statistically increased incidence of haemangiosarcomas in males, supported by rare haemangiosarcomas (though not significant) in females of the Atkinson study. Three studies (Wood et al. 2009b, Sugimoto 1997 and Kumar 2001) found significantly increased incidence of malignant lymphomas in males.

5.0 CARCINOGENIC POTENTIAL IN ANIMALS

As detailed above, EPA has failed to report several statistically significant tumor findings. When these are considered, the animal data are much more persuasive than suggested in EPA's discussion (EPA 2016, pp. 95-96).

Significant increases in particular tumor types (trend and/or pairwise) that appear in more than one study, strain, sex and/or rodent species are accorded greater weight, as are rare and severe (malignant) tumors (EPA 2005, 2-21, 2-22). Liver tumors were found at elevated rates in two studies in different strains of male rat (Sprague-Dawley and Wistar). Renal tumors were found at statistically increased rates in males in three studies of two strains of mouse (CD-1 (2) and Swiss albino (1)). Two mouse studies found statistically significant increases in haemangiosarcomas in males, supported by their presence (though not significant) in females of one study. In addition, one poorly reported study (Atkinson et al., 1993a) found haemangiosarcomas in rats in tissues in which their presence is quite rare. Finally, malignant lymphomas were found at statistically elevated rates in males of three mouse studies involving two strains (CD-1 and Swiss albino). In most cases, historical control data support the biological relevance of these statistically significant findings. This description is not meant to discount findings of tumor types that were found in only one study or rodent strain, which are not summarized here but could still have biological relevance.

I addressed EPA's misapplication of its Guidelines above. Here we reiterate that EPA's attempt to discount animal tumor findings at doses of 1,000 mg/kg bw/day because they exceed anticipated human exposure levels (p. 96) is entirely illegitimate, and not supported by either its Guidelines or any other accepted guidance for the conduct and interpretation of animal toxicology studies. As discussed below, the relevance of an animal-based hazard assessment to human risk is evaluated only later, after full assessments of dose-response and exposure (EPA 2005, Sections 3 & 4), neither of which was undertaken in this Issue Paper.

Clearly, the animal toxicology studies provide sufficient evidence to establish a causal relationship between glyphosate exposure and increased incidence of tumors in multiple tissues.

6.0 OVERALL ASSESSMENT OF CARCINOGENIC POTENTIAL

EPA's Guidelines state: "In these cancer guidelines, tumors observed in animals are generally assumed to indicate that an agent may produce tumors in humans" (EPA 2005, 2-22). Thus, the animal findings alone suggest that glyphosate exposure poses a carcinogenic ***hazard*** to humans (although not necessarily a ***risk***, discussed below). The human epidemiology studies point in the same direction for non-Hodgkin's lymphoma. Three meta-analyses yielded odds ratios of 1.5 (Schinasi and Leon 2014), 1.3 (IARC), and 1.3 (Chang and Delzell 2016), all with lower-bound confidence intervals at 1.0 or above. De Roos et al. (2003)'s integrative assessment of three studies yielded among the highest odds ratios (OR = 2.1 (CI = 1.1-2.0)) logistic regression controlling for co-exposure to other pesticides (EPA 2016, p. 56). De Roos et al. (2003) acquired cases during a period of high glyphosate usage rates/exposure (1979-1986), thus supporting the higher risk estimate versus studies like De Roos et al. (2005) conducted later, when glyphosate usage rates/exposure were lower (see Section 1.2 above). While not all studies agree, the weight of the human evidence demonstrates a plausible causal relationship between glyphosate exposure and NHL, even if chance/bias cannot be definitively ruled out.

The human epidemiological studies should also be considered in the context of the animal data. According to EPA's Guidelines: "epidemiological studies that show elevated cancer risk for tumor sites corresponding to those at which laboratory animals experience increased tumor incidence can strengthen the weight of evidence of human carcinogenicity" (EPA 2005, 2-2, 2-3). Malignant lymphomas were among the strongest findings in animal studies, while epidemiology suggests glyphosate exposure is a risk factor for malignant lymphomas in humans.

How should glyphosate be classified? The Guidelines discuss criteria for assignment of various "descriptors" (EPA 2005, 2-53 to 2-58). This classification system (e.g. likely or not likely to carcinogenic) is based purely on the ***hazard*** assessment, prior to the consideration of dose-response or human exposure levels required for a full risk assessment. On this basis, "likely to be carcinogenic to humans" best fits the evidence. Criteria for assignment of this descriptor include "an agent that has tested positive in animal experiments in more than one species, sex, strain, site, or exposure route, with or without evidence of carcinogenicity in humans" or "a

positive tumor study that is strengthened by other lines of evidence, for example … plausible (but not definitively causal) association between human exposure and cancer" (EPA 2005, 2-55).

What would a determination that glyphosate has carcinogenic potential entail? First, it would not lead to the banning of glyphosate. Many pesticides that EPA has designated "likely to be carcinogenic to humans" or "probable human carcinogens" are in widespread use today. These include acetochlor, carbaryl, chlorothalonil, clodinafop, cyproconazole, isoxaflutole and tribufos. For their cancer hazard classifications, see EPA (2004). For their usage, consult the U.S. Geological Survey's Pesticide National Synthesis Project.[13] Acetochlor is one of the most heavily applied herbicides in the country, with usage rising in response to glyphosate-resistant weeds, and topping 40 million lbs. in 2014. The use of isoxaflutole will likely rise considerably with the 2017 introduction of Balance GT soybeans, which are resistant to both isoxaflutole and glyphosate, and are being pre-marketed as a means to control herbicide-resistant weeds (Bayer 2016).

Only if glyphosate were to be classified as "carcinogenic to humans" or "likely to be carcinogenic to humans" would EPA conduct a dose-response assessment, which "estimates potential risks to humans at exposure levels of interest" (EPA 2005, 3-1, 3-2). If this stage of the risk assessment is reached, animal data would be used to construct a dose-response curve and cancer slope or potency factor (EPA 2005, Section 3; Subramaniam et al. 2006).

In 1985, EPA utilized animal data to calculate a cancer slope factor (Q*) for glyphosate (EPA 6/19/85, pdf p. 8). A committee of the National Research Council estimated the oncogenic risk from dietary exposure to glyphosate along similar lines (NRC 1987, Table 3-17, p. 76). Dietary exposure has of course increased substantially since that time. After a full assessment of human exposure, both for the general population and subpopulations (EPA 2005, Section 4), EPA would then characterize the carcinogenic risk of glyphosate, which would "bring[] together the assessments of hazard, dose response and exposure to make risk estimates for the scenarios of interest" (EPA 2005, Section 5).

[13] See http://water.usgs.gov/nawqa/pnsp/usage/maps/compound_listing.php?year=2014&hilo=L.

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