Slide Narrative

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The opinions expressed here are my own. Besides doing several other things, I serve as a consultant to several law firms in the US involved in glyphosate litigation.

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These are the three main points I will be addressing during this presentation. I will return to them at the end of my talk.

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The evaluation of the scientific evidence for any substance involves three major classes of data; epidemiology studies, experimental animal carcinogenicity studies and mechanistic studies. In 15 minutes I do not have the time to cover all of these data so I will focus on the animal cancer bioassays to illustrate some key issues.

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Typical animal cancer bioassays will expose animals (generally rats or mice) to a chemical for a substantial proportion of the animal’s life then kill the animal and examine its organs and tissues for tumors. There are guidelines on how to conduct and analyze these studies. These studies are conducted in a way that controls for everything in the animal’s environment leaving only the exposure to explain differences in tumor formation between control and exposed animals.

Studies generally use four groups of animals, one group receiving no exposure (control) and the remaining three groups are test animals, with each group receiving different dose exposures to the chemical. Animals are randomly assigned to these dose groups. Doses are generally chosen that are not overtly toxic to the animals using a 90-day experiment with the same rat or mouse strain.

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There are a total of 21 animal carcinogenicity studies available for evaluating the carcinogenicity of glyphosate. Most reviews have concluded that 9 of these studies have limitations that exclude them from consideration leaving 12 studies for the evaluation. There are 7 studies in rats and 5 studies in mice. They were conducted at different times spanning 26 years, they use different strains and they expose the animals for different durations. Allow of these factors can affect the results and must be carefully included in any evaluation.
There have been a large number of reviews of glyphosate over the years. I want to begin my discussion of these data by first looking to see what tumors in what studies have been relied upon. These six evaluations will be the focus of this discussion. I have grouped the EFSA and EChA reviews together since they seem to have used exactly the same set of tumors.

In 2013, the German BfR released their Renewal Assessment Report (the RAR) on glyphosate. They discussed two tumor findings in male mice, malignant lymphomas seen in two different mouse studies. The M after malignant lymphoma stands for male animals. F will later be used for female animals. They did not discuss any tumors from the earliest studies, but simply referred the reader back to an earlier review of glyphosate. I will go through the studies sequentially and the number in the upper right corner of the slide is a count of all of the sights that have been mentioned in any evaluation on the slide.

In early 2015, Greim and colleagues published a review of these studies with funding from industry. In addition to the malignant lymphomas seen in the RAR report, they also noted increases in kidney tumors, lung tumors, and malignant lymphomas in a third mouse study. In this table, the blocks in red represent the tumor sites that were not discussed in the report and an X indicates it was discussed. For example, the RAR did not discuss positive findings for lung adenocarcinomas in the 2009 study, but Greim and colleagues did.

In 2015, IARC reviewed some of the animal carcinogenicity data for glyphosate but not all of the data due to restrictions on what information from these studies was available. IARC discussed three tumor sites in mice, finding hemangiosarcomas in the 1993 study that had not been discussed previously. We are now at 7 tumor sites.

EFSA in 2015 and EChA in 2017 released their final evaluations of the glyphosate literature. They did not discuss the lung adenocarcinomas findings from the 2009 study but did discuss all of the other findings. In addition, they identified two additional tumors in the 1997
study that had not been discussed previously. That now brings us up to a total of 9 tumor sites discussed.

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EPA in 2016 released their draft issue paper on glyphosate. EPA did not discuss three of the previously identified tumor findings but found one additional tumor that had not been discussed previously, hemangiomas in female mice in the 2009 study. So now we are at 10 tumor sites.

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In the last two years, I have systematically gone through these data to identify any statistically significant findings that might have been missed in the other evaluations. I found three additional tumors that had not been discussed in any of the previous evaluations bringing our total to 13 findings that should be discussed. Of the total of 13 findings that should have been identified and addressed by EFSA and EChA, they only discuss 8.

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The same sort of evaluation can be done for the rat studies. Here, there are a larger number of studies and hence a larger number of tumor sites with a significant increase in tumors as a function of glyphosate exposure. In this case, there are 7 tumors not discussed in any of the evaluations and EFSA/EChA have only discussed 9 of the total 21 tumors. The full set of slides for the rat studies are available as extra slides attached to this slide presentation.

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So, to summarize, there are a total of 34 tumors in these 12 studies that should have been identified and discussed. Ten of these statistically significant tumor findings have not been discussed in any of the existing reviews. EFSA and EChA discussed exactly half of the statistically significant tumor sites in these studies. EPA was not much better, only discussing 18 of the 34 tumor sites.

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You may ask yourself, why is this so important? Findings of statistical significance are one of the key factors used to determine which tumors are increasing as the dose of glyphosate is
increased. A lot of other issues need to be considered to decide if that finding is a real finding or just due to random chance, but if you don’t know that glyphosate increases the risk of getting the tumor, you won’t know to look at these other aspects. In their response to my letter of May 28 of this year to President Juncker, EFSA and EChA stated that they do not routinely examine the original study reports in depth for additional tumors. I assume they also do not reanalyze the data. Without reanalyzing the data, they are assuming that the presentation of the data by the industry contract lab is both accurate and comprehensive. If it is not, as is the case here, the results are likely to be biased in favor of fewer significant tumor findings.

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It is not possible for me to discuss all of these different tumors in a 15-minute presentation. Instead, I will focus on hematopoetic system tumors since NHL in humans falls into this category. In mice, there are four tumors in this same organ system to consider. Are any of these similar to NHL in humans?

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About 85% of the tumors that make up the class of NHL are B cell lymphomas with the largest subclass of B lymphomas being diffuse large B cell lymphomas. If you study the literature broader than just glyphosate, you see that B cell lymphomas in mice are used as a model for B cell lymphomas in humans. This means that the two diseases are close enough in phenotype and function that if, for example, you wanted to develop a new therapy for B cell lymphomas in humans, you would first use the mouse to see if it is both efficacious and safe. Since B cell lymphomas in mice are classified as malignant lymphomas, this tumor is a very close match for NHL in humans. Thus, there is a strong biological link between these two.

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Both EFSA and EChA concluded the malignant lymphomas in mice were not caused by glyphosate. They gave several reasons. First, they conclude that tumors falling within the range of the historical rates of these tumors in controls should be excluded. For any given study, the most appropriate control is the concurrent control; I will talk more about this later. But generally, while the OECD Guidelines on how to conduct and analyze these studies talk about a number of more rigorous analyses for using historical controls, they do allow for some informal evaluations. However, they warn against the use of the range for historical control evaluations because it can be very misleading and mischaracterize a positive finding as
negative. They suggest a different approach using the “inter-quartile” range and, in this case, the findings in the experiments showing increases in malignant lymphomas are outside the range of historical control response.

NOTE: Historical controls are generally the historical collection of tumor responses from untreated control groups from studies in the same laboratory within two to three years of the study being evaluated.

Another reason to exclude a result was seeing no significant pairwise comparisons. This is actually not surprising since the trend test generally has much higher ability to identify a true-positive response than dose apairwise test. Most agencies, however, will reject chance if either test is positive. NTP presents both a trend test and pairwise comparisons but generally bases their decision regarding statistical significance on the trend test.

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Another reason they give for excluding these findings is that there was potential general toxicity in the highest dose group in the 1997 study. Toxicity would present itself as either an increase in mortality in this group and/or a significant reduction in body weight without a significant reduction in food consumption. As shown in EFSA’s evaluation, that has not happened here.

Another reason they give for excluding these findings is that the results were only positive in males and not in females. However, there are many carcinogens that are positive in only one sex such as the known human carcinogen 4-Aminobiphenyl.

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The final reason they give for excluding these findings is that they are not consistent across the four studies. Here I have provide you with the actual tumor data. Now, several things should be noted in this table. First, there are studies of 18 month duration and studies of 24 month duration. Why does this matter? Just like in humans, as mice age, they get more tumors just by chance. Comparing tumor rates in mice exposed for 18 months versus those exposed for 24 months is similar to comparing tumor rates in 55 year old humans to tumor rates in 75 year old humans; they are different. The second thing to notice is that the two 18 month studies are the most recent studies and the studies range over 26 years. A lot can change in 26 years; how you
house the animals, the type of bedding, the feed, the genetics of the animals, etc. In my 37 years at the US National Toxicology Program we changed these factors several times. For example, in 2003, our laboratories and most other toxicology laboratories changed the diet because the fish oil used in the diet contained small amounts of the very potent carcinogen, dioxin. This is one of the reasons the concurrent control is the most appropriate; it received the same diet, the same housing, the same bedding, it has the same genetics, etc. as the treated animals. Clearly, in the 18-month studies the results are highly statistically significant. The pooled analyses demonstrate agreement between the studies. One is a simple pooling of the data into one larger dataset and the second uses a general linear model and accounts for potential differences between the studies. The 24 month studies appear to be different although one is almost statistically significant.

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I hope I have provided evidence supporting these three points; The current process is scientifically flawed, it is time to have an independent panel of scientists evaluate the way in which the science is reviewed, there is a need for the regulatory agencies to reanalyze the data, and there is a need to publically release all of the analyses and data to improve the transparency of this process. The issues I raised here are not all of the problems I have found with the assessment but demonstrate some of them. This was just the evaluation for carcinogenicity. What about toxicity to the reproductive system? Toxicity to the endocrine system? Do they have problems as well? I don’t know because I do not have access to those data. And what about the 450-plus other pesticides that have been reviewed? If there is one thing that is clear 2.5 years after the IARC review, it is that without that review, we would not know the extent to which glyphosate can cause tumors in mice and rats; it is only because the original industry-sponsored data were released that others are able to analyze the data and identify tumors that were missed by all of the regulatory agencies. This is a direct consequence of the IARC review.