SEAPHS
SAMSEL ENVIRONMENTAL AND PUBLIC HEALTH SERVICES

April 19, 2018

United States Environmental Protection Agency
Environmental Protection Agency Docket Center (EPA/DC), (28221T)
Office of Pesticide Programs
1200 Pennsylvania Avenue
NW, Washington, DC 20460-0001

Re: Docket number ID: EPA-HQ-OPP-2009-0361-0066
Response to EPA Glyphosate Decision

Subject: Raising the issue of Lymphomas and Hemangioendotheliomas in Monsanto's Glyphosate studies and my September 24, 2012 letter of warning to the agency concerning glyphosate and the rise in modern diseases

Dear members of the US EPA Office of Pesticide Programs,

The US EPA, EFSA and EChA have failed to identify all of the statistically significant cancer findings of the Monsanto long-term chronic rodent studies for glyphosate.

In a letter dated May 28, 2017, by Dr. Christopher J. Portier to the President of the European Commission Jean Claude Junker, Portier revealed eight additional tumor sites with significant ($p<0.05$) increases due to glyphosate exposure in carcinogenicity studies cited by EFSA and EChA. In this letter he stated: "In summary, after numerous scientists from EFSA, from EChA, from BfR and from the Glyphosate Task Force have reviewed and evaluated this massive amount of data, there are still serious omissions in the way in which these data have been assessed and reported."

I concur with my colleague and now raise the issue of additional statistically significant tumors that I have found during review of the Monsanto studies. In June 2017, I appeared before the California

OEHHA and presented data on malignant lymphoma found in female rats, data extracted from the Monsanto Lankas & Hogan study (1981). I present that data and additional data to you today as part of this communication. These data found significant lymphomas in fourteen different tissues of female rats, but not in the female control group of glyphosate treated animals. *See attachment at end of letter*

Additionally, I enclose statistically significant data that I gleaned of malignant and metastatic Hemangiomas and Hemangioendothelioma tumors found in mice. (1) Malignant Hemangioendotheliomas found in mice administered glyphosate. This data is from Monsanto's unpublished study "A Chronic feeding study of Glyphosate (Roundup Technical) in mice." (2) I believe it should have been included as additional evidence of the carcinogenicity of glyphosate (N-phosphonomethyl glycine). It appears that Monsanto, the US EPA Working Group, EFSA and EChA have previously ignored and not cited these important tumors in the carcinogenicity discussion.

I am continuing to review the data of all tumors from the actual pathology reports and comparing them to Monsanto's study summaries of findings of tumors found during chronic administration of glyphosate. I raise this particularly issue, in light of the recent U.S. House science committee hearing which questioned the "scientific integrity" of the International Agency for Research on Cancer (IARC), the World Health Organization's cancer agency findings on glyphosate.

The Congressional House Science, Space and Technology committee hearing seemed to lack credibility of basic facts. In Dr. Robert Tarone's testimony, he discussed the Hemangioendothelioma tumors found in the Monsanto mouse study of 1983. Hemangioendothelioma is a rare sarcoma showing endothelial differentiation. He stated that Monsanto pathologists found one hemangio tumor in the low dose group and one hemangio in the mid dose group and none in the high dose group and further remarked that the high dose group were fed glyphosate as 3% of the diet.

Tarone's statements to the SST committee on the Knezevich A, Hogan G (1983) "A chronic feeding study of glyphosate (Roundup Technical) in mice," lacked credibility of the basic facts, as evidenced by the data I have enclosed. The mice of this study, received 1, 5, and 30 mg/kg doses of glyphosate technical acid in the diet over the course of 18-months or

as expressed in the study in parts per million as 1,000, 5,000, and 30,000 ppm. These data can be viewed at the end of this communication in the enclosed table titled: Malignant Hemangioendotheliomas found in mice administered glyphosate.

These are the tumor data which I extracted from this study. Male and female mice were both affected in all three treated groups and particularly the female animals of the 3 dose groups and in multiple types of tissue. Data for kidney tumors from this study were relied on by the US EPA and it is my professional opinion that the additional data from this study can be relied upon as the *lowest, reliable animal data of any glyphosate study with significant* events for all three dose quantities.

Coincidentally, lymphomas and hemangiomas are among the most common tumors now found in domestic pets both in dogs and feline cats. Popular brands of cat and dog food are ubiquitously contaminated with glyphosate residues. These were first analyzed by Samsel in 2015 for glyphosate using HPLC MSMS. That data can be viewed in Glyphosate, pathways to modern diseases IV: cancer and related pathologies published in the January 2015 Journal of Biological Physics and Chemistry (6) the tables of which are also included below. “The American Veterinary Medical Foundation notes that “Cancer is the leading cause of death in older pets, accounting for almost half of the deaths of pets over 10 years of age.” (6)

According to the NIH GARD website, “The term hemangioendothelioma describes several types of vascular neosplasms and includes both non-cancerous (benign) and cancerous (malignant) growths. The term has also been applied to those that show "borderline" behavior, intermediate between entirely benign hemangiomas and highly malignant angiosarcomas. Hemangioendotheliomas are caused by abnormal growth of blood vessel cells, although the exact underlying cause for the abnormal growth is unknown. They can also develop in an organ, such as the liver or lung. They usually grow slowly and can sometimes spread to other tissues in the body (metastasize). Examples of types of hemangioendotheliomas include spindle cell hemangioma; papillary intralymphatic (Dabska tumor); retiform; kaposiform; epithelioid; pseudomyogenic (epithelioid sarcoma-like hemangioendothelioma); and composite.”(7)

According to the Children's Hospital in Los Angeles, CA, "Hemangiomas are the most common vascular anomaly and the most common tumor of childhood and infancy." (8) Hemangioendotheliomas, AKA Epithelioid Hemangioendothelioma is a rare type of vascular tumor which represent "about 2% of the soft tissue tumors found in children and teens" as noted by St Judes Hospital. (9)

In another instance during the Congressional hearing, references were made of the EPA task force reviewers determination of tumors found in the kidneys of the mice of the K&H study. The agency stated that there were no other tumors found in the kidneys other than the renal tubule adenomas referred to in the 1985 argument which ensued between Monsanto and the US EPA. (2,3,4) This statement is also false, as there were other tumors in the kidney data which reviewers did not mention in the report summary.

I found additional kidney tumors which were not discussed. In fact, one of the types of tumors found in the kidneys of the mice was Lymphoblastic lymphosarcoma with leukemic manifestations. These occurred noticeably in both male and females and more frequently than in the control animals. In males of groups 1-4 beginning with the control 1/49(2%), 3/49(6%), 2/50(4%) and 2/50(4%) respectively and in female animals as 1/50 (2%), 2/50 (4%), 3/50(6%) and 1/50(2%) respectively and in a second kidney of the high dose females an additional tumor 1/50(2%).

I would like to relay to the agency a few of the observations I have made of Monsanto's chronic feeding studies conducted in mice and rats. First, concerns their diet and incidence of cancers. The diets used in the Monsanto experiments were Purina chows and are void of natural folate vitamin B9. I checked with Purina and they haven't changed these formulations since their virtual inception, well before the Monsanto Glyphosate studies were conducted for the registration process. Purina lab chows contain synthetic folic acid as a B9 folate replacement and also choline chloride. Natural folate (vitamin B9) from a vegetative source thermally degrades so manufacturer's attempt replacement with folic acid a synthetic form. However, the molecules are not the same they are different and do not necessarily behave the same biologically. I would also add that disruption of beneficial bacteria by glyphosate in the digestive tracts of these animals would also reduce the natural form of folate B9 manufactured by these symbionts further creating a deficiency. *The lack of natural folate B9 in the cells is associated with cancer.*

Chelators like glyphosate disrupt calcium signaling as outlined in our papers which also suppresses the immune system response including tumor suppression.

Thus, the induction of cancers in dogs and cats fed diets contaminated by glyphosate can be readily apparent. I was the first to make this connection of glyphosate as a causal agent in the rise of cancers seen in our pet population several years ago, which includes cats and dogs. My laboratory findings were disseminated by veterinarians in articles about cancer in pets. Some of my data was published in 2015 in the Samsel & Seneff paper Glyphosate, pathways to modern diseases IV: cancer and related pathologies.

I analyzed many popular brands of cat and dog food using HPLC MSMS to make determinations of glyphosate contamination and found all pet foods ubiquitously contaminated with glyphosate. I found the chows used to feed laboratory mice and rats ubiquitously contaminated. I used HPLC to test for choline chloride and folic acid as folate (B9) and found the rodent diets depleted and void of any detectable level of folate B9. This raises the issue of glyphosate interference in all laboratory studies conducted today for all chemicals. In my honest opinion, the cancers found in the control animals of the Monsanto studies were enhanced by the of lack of natural folate vitamin B9. The increases of many cancers in the glyphosate treated animals thus become more evident and possibly with what we see today with increased incidence. *I warned the agency in 2012 that glyphosate could cause severe birth defects including neural tube defects and spina bifida as related to folate deficiency and even infertility and sexual dysfunction citing its disruption of B vitamins.*

In Glyphosate IV I wrote: “The American Veterinary Medical Foundation notes that “Cancer is the leading cause of death in older pets, accounting for almost half of the deaths of pets over 10 years of age.” According to the Morris Animal Foundation, established in 1948, one in four dogs will die of cancer and over 22,000 cats will be diagnosed with aggressive sarcomas. Oral cancer squamous cell carcinomas are now found in cats and lead to the destruction of the jawbone. Mammary tumours, a common cancer found in dogs and cats, are also on the rise. We suspect that glyphosate may be a causal agent related to the rise of pet cancers, and used HPLC to analyze 9 popular brands of dog and cat food. We

Table 15. Glyphosate and AMPA residues found in various dog food and cat food products, as measured from samples tested by the authors.

	Glyphosate /mg kg^{-1}	AMPA /mg kg^{-1}
Purina Cat Chow Complete	0.102	0.12
Purina Dog Chow Complete	0.098	0.076
Kibbles-n-Bits Chefs Choice Am Grill	0.30	0.24
Friskies Indoor Delights	0.079	0.11
9 Lives Indoor Complete	0.14	0.12
Rachael Ray Zero Grain	0.022	Trace (< 0.02)
Iams Proactive Health	0.065	Trace (< 0.02)
Rachael Ray Nutrish Super Premium	0.14	0.14
Purina Beyond Natural - Simply Nine	0.047	0.031

found significant levels of both glyphosate and AMPA in all pet foods tested (Table 15). “

Table 14. Evidence of glyphosate contamination, and levels of folate and choline, in Purina rat chow products as determined from authors' own analyses.

	Glyphosate /mg kg^{-1}	AMPA /mg kg^{-1}	Folate /mg g^{-1}	Choline /mg g^{-1}
Purina Rat Chow 5002	0.65	0.35	0	4.827
Purina Chow 5K75	0.57	0.27	0	5.328
Purina Chow 5LG3	0.37	0.10	0	5.919

“A synthetic form of choline, choline chloride, has been added to formulated lab chow diets for decades, as indicated from historical references available from manufacturers such as Purina. A 2010 European patent application describes the addition of choline chloride to glyphosate formulations to act as a bioactivator and to enhance penetration of glyphosate into the cells of the target weed [35]. A study of 47,896 male health professionals in the US found that high choline intake was associated with an increased risk of lethal prostate cancer [36]. Our samples all tested positive for choline chloride (see Table 14).” (Samsel & Seneff 2015)

I also raise the issue of Glyphosate nitrosamine contaminants. There are no safe levels of the N-Nitrosamines of glyphosate found in every glyphosate-based product and the nitrosamines of which are also created from glyphosate in vivo. N-nitrosamines given by oral administration are known to produce hemingioendothelioma tumors. (10, 11, 12).

There are no safe levels of the N-nitrosamines of glyphosate. Glyphosate is a synthetic amino acid and analogue of our canonical amino acid glycine and participates in plant and animal biology. N-nitrosamines of glyphosate are found in both animals and the soil of fields where glyphosate is used.

The N-nitrosamines of secondary amines are known to be carcinogenic. The nitrosamines of glyphosate are formed on a secondary amine. I now raise the issue of the N-nitrosamines of glyphosate of which there are several, because they are carcinogens and have all been essentially ignored. It appears that Monsanto and the US EPA have hidden the N-nitrosamines of glyphosate from discussion even to the point of editing and redacting data from crucial documents concerning a number of N-nitrosamines of glyphosate. I am fortunate to have received all of the Monsanto documents on the N-nitrosamines of glyphosate from the US EPA, and I can speak directly to this issue.

The nitrosamines of glyphosate are also synthetic amino acids which may participate in biology with adverse consequences. One part per trillion of glyphosate has been demonstrated to induce the growth of breast cancer cells. One part per trillion (1 ppt) may not seem like a lot. However, in one microgram of glyphosate (1 ppb) there are over 3.564 trillion molecules of glyphosate or over 3 billion in 1 ppt, participating in random collisions at the molecular level.

The US EPA set a limit of 1 ppm (1,000 ppb) of N-nitrosoglyphosate in Roundup products. Monsanto trade secret documents clearly show that nitrosamines of glyphosate increase in vivo over and above what is found in the products and you may refer to the tables in the peer-reviewed paper Glyphosate pathways to modern diseases IV: cancer and related pathologies Table 13 to view some of this information. Glyphosate actually increases in concentration over that measured in the original dose solutions of 14-C experiments. This is a sobering fact that must not be taken lightly. Like the drug TAMOXIFEN, Glyphosate does not behave in a dose dependent fashion, as it is non monotonic. Today in risk assessment we now realize that there are two types of agents that can be deleterious to human and animal biology. Those that may have a threshold for intake and exposure and those that cause harm at any level above zero as noted by Kinoshita et al (Hormesis in Carcinogenicity of Non-genotoxic Carcinogens, J Toxic Pathol 2006; 19 : 111-122).

For convenience, I have provided direct copy here of relative portions of my work which speak to the issues involving the nitrosamines of glyphosate and include them as part of this communication. The reference numbers have been left in with the text and you may access them in the published papers at ResearchGate the links of which are provided at end of this letter. See Samsel & Seneff: Glyphosate pathways to modern diseases IV: cancer and related pathologies

The abstract which mentions a nitrosamine of glyphosate reads in part: ”Glyphosate has a large number of tumorigenic effects on biological systems, including direct damage to DNA in sensitive cells, disruption of glycine homeostasis, succinate dehydrogenase inhibition, chelation of manganese, modification to more carcinogenic molecules such as N-nitrosoglyphosate and glyoxylate, disruption of fructose metabolism, etc.”

Please see page 128 of this paper for the actual real world concentrations of N-nitrosoglyphosate found in the dose solutions of glyphosate and used in 14-C radio labeled studies, as well as increasing concentrations found in faeces and urine of test animals administered this synthetic amino acid. I would also note that the synthetic amino acid glyphosate is an amphiphilic Zwitterion. *Glyphosate is an electrophile***,** a Lewis acid and it does affect DNA as evidenced by its ability to modulate genes in microbial studies.

“Of all of the nonbasic compounds found during analysis of excreta, AMPA followed by N-nitrosoglyphosate were most prevalent. Total N-nitrosoglyphosate levels found in the animals ranged between 0.06–0.20% of the given dose. Faecal samples contained 0.10–0.32% and urine 0.06–0.15% of N-nitrosoglyphosate. Stability studies revealed that the majority of the N-nitrosoglyphosate found in the faeces was not completely due to presence of the compound as a contaminant of glyphosate, nor was it due to animal metabolism, but rather was due to the chemical reaction of glyphosate with nitrites
contained in the excreta. Glyphosate readily reacts with oxides of nitrogen (e.g., NO2) to form the metabolite N-nitrosoglyphosate. This engenders concern because N-nitroso compounds are carcinogens. Nitrous acid occurring in sweat excreta of the skin could be problematic in the presence of glyphosate and may be responsible for the rise of some skin cancers. N-nitrosoglyphosate, the product of chemical reaction between glyphosate residues and nitrites in the colon, may in fact be a

causal agent in the alarming increase in colorectal cancer. We discuss N-nitrosoglyphosate in §9.

Colvin, Moran & Miller [27] evaluated the metabolism of 14C-AMPA in male Wistar rats. A 6.7 mg/kg dose of radio labelled AMPA was administered orally, of which 20% was found unchanged in the urine of the animals and 74% in the faeces. Recovery from excreta totalled 94% of the dose. In another study, Sutherland [28] fed Sprague Dawley rats a single radiolabelled dose of N-nitrosglyphosate and successfully quantified the metabolite in the urine and faeces. Male and female animals received 3.6 mg/ kg and 4.7 mg/kg, excreting 2.8% (faeces) 88.7% (urine) and 10.7% (faeces), 80.8% (urine) respectively. Both male and female rats retained 8.5% of the N-nitrosoglyphosate dose, while 90.5% was eliminated in excreta."

9. N-NITROSOGLYPHOSATE AND N-NITROSOSARCOSINE

"As was shown by Monsanto's own studies [26], glyphosate readily reacts with nitrogen oxides to form N-nitrosoglyphosate (NNG), which is of great concern due to its toxicity [105]. N-nitroso compounds (NOCs) can induce cancer in multiple organs in at least 40 different animal species, including higher primates [106–108]. In *in vitro* studies on human liver slices, the mechanism of action was shown to be nucleic acid alkylation [109]. Schmahl and Habs commented: "N-nitroso compounds can act carcinogenically in a large number of animal species; there is no rational reason why human beings should be an exception, all the less so since in vitro experiments have shown N-nitroso compounds are metabolized in the same way by human livers as by the livers of experimental animals" [108, p. 240]. Several different nitrosylated compounds have been targeted as potential carcinogenic agents, although it is conceded that the long lag time between exposure and tumour development makes it difficult to recognize the links [110]. Dietary N-nitrosyl compounds especially are thought to increase the risk of colon cancer and rectal carcinoma [111, 112].

The Food and Agricultural Organization of the United Nations (FAO) has set a strict upper limit of 1 ppm NNG [113]. The accepted methodology for measuring contamination levels, proposed by Monsanto in 1986 [114], has complicated instrumentation and operation conditions and is relatively insensitive [105]. New advanced methodologies offer safer and more reliable testing methods [115, 105]. One of the pathways by which

some bacteria break down glyphosate is by first using carbon phosphorus lyase (C-P lyase) to produce sarcosine as an immediate breakdown product [89, 116]. Nitrosylated sarcosine is well recognized as a carcinogenic agent. Injection of 225 mg/kg of nitrososarcosine into mice at days 1, 4 and 7 of life led to the development of metastasizing liver carcinomas in later life in 8 out of 14 exposed animals [117].

Elevated levels of sarcosine are also linked to prostate cancer, particularly metastatic prostate cancer [118]. An unbiased metabolomic survey of prostate cancer patients identified elevated levels of serum or urinary sarcosine as a marker of aggressive disease [119] (prostate cancer is the most commonly diagnosed cancer in men in the USA, and it afflicts one in nine men over the age of 65 [120]). In both in vitro and in vivo prostate cancer models, exposure to sarcosine, but not glycine or alanine, induced invasion and intravasation [119]." **Sarcosine is also a metabolite of glyphosate.**

For references in the following text please see Samsel & Seneff: Glyphosate pathways to modern diseases VI: Prions, amyloidosis and autoimmune neurological diseases

3. Glyphosate As A Glycine Analogue

"…N-nitrosoamino acids form a reasonable model for N-nitrosoglyphosate, a carcinogenic derivative of glyphosate that was of concern to the EPA during Monsanto's early studies. N-nitrosoproline is particularly relevant because proline, like glyphosate, has an extra carbon atom bound to the nitrogen atom. With respect to non-coding amino acids, and especially the incorporation of N-nitrosoamino acids into peptides and proteins. R.C. Massey remarked: "In addition to their presence as free N-nitrosoamino acids, species such as N-nitrosoproline (NPRO) and N-nitroso-4-hydroxyproline (HONPRO) may exist in a peptide- or protein-bound form as a result of N-nitrosation of an N-terminal imino acid residue" [62]. Tricker et al. [63] and Kubacki et al.[64] devised high performance liquid chromatography–thermal energy analyser (HPLC–TEA) techniques for analysis of multiple dipeptides with a nitrosylated N-terminal, including N- nitrosoprolylalanine (NPROALA),N-nitrosoprolyl-4- hydroxyproline (NPROHOPRO) and N-nitrosoprolylglycine (NPROGLY) [63, 64]. Tricker notes that the average recoveries for NPROALA, NPROHOPRO and NPROGLY, 200 μg of

which was added to cured meat, were between 69 and 88%. Tricker also used the method to analyse the nitroso tripeptide N-nitrosoprolylglycyl glycine [65].

Nitrosamines of glyphosate (N-phosphonomethylglycine), its salts and esters include: N-nitrosoglyphosate (NNG (Monsanto CP 76976), N-nitrosoiminodiacetic acid (NNIDA), N-nitrosoglyphosate sodium salt (NNGNa), N-nitrosoglyphosate isopropylamine ester (NNGIPA), N-nitrosoglyphosate potassium salt (NNGK), the metabolite N-nitrosoAMPA (NNAMPA), the metabolites N-nitrosodimethyl amine (NDMA) and N-nitrosarcosine (NSAR), which occur in glyphosate products or may be generated in vivo or in soils and waterways. N-nitroso compounds derived from secondary amines are considered carcinogenic.

Monsanto glyphosate documents reveal analysis and quantification of five nitrosamines of concern [61]. Out of six lots of Roundup analyzed for NNG, four lots contained NNG residues of 0.61 to 0.78 ppm and two lots had residues from 0.22 to 0.40 ppm NNG. Analysis of six lots of Monsanto Rodeo revealed NNG residues in the range 0.13–0.49. ”

The document by Hirsch reference 61 above, also shows significant levels of other nitrosamines of glyphosate one of which was equivalent to the levels found of N- nitrosoglyphosate. Monsanto and the US EPA have suppressed these documents. I find that the hiding of these documents and this information is most disturbing. The pubic and scientific community deserve to know and have access to these important documents.. SEE: Hirsch, R.H., Augustin, D.J. Nitrosamine analyses of Roundup herbicide, Rodeo herbicide, MON 0139 and Polado Technical (unpublished study RD835). St Louis, Missouri: Monsanto Agricultural Company (4 November 1987).

Of the many types of cancers detailed in the Monsanto animal studies the data of which is shown in Glyphosate pathways to modern diseases IV, I draw your attention to the data on malignant lymphoma. Statistically significant data was found in the female rats of the1981 Lankas and Hogan study and I have extracted that data and posted it to ResearchGate for convenience. A copy is included at the end of this letter. You will note that malignant lymphoma occurred in 14 different tissues. You will also note that the female control rats not fed glyphosate were not stricken by this type of malignant cancer. Only the glyphosate treated rats of this sex and groups receiving glyphosate in the diet got

malignant lymphoma. Glyphosate can be seen in this light, as a causal agent of malignant lymphoma. This is not coincidence.

A thorough consideration of Glyphosate cannot be had without a deep investigation and understanding of the nitrosamines of glyphosate which are carcinogens. Make no mistake, all Roundup glyphosate based herbicide products, as well as ingested glyphosate residues are responsible for carcinogenic N-nitrosamine compounds for which human and animal populations are and will be exposed. Glyphosate and its nitrosamines do not belong in any biology.

Again, one microgram of glyphosate technical acid (N-phosphonylmethyl glycine) contains 3.561 trillion molecules each capable of integrating with a protein altering shape, folding and function.

Based on my latest laboratory work, I have found that Glyphosate integrates with and becomes part of globular and structural proteins of humans and other animals. I have found glyphosate integrated with digestive enzymes which include the enzymes pepsin, trypsin and lipase. Glyphosate totally inhibits the lipase enzyme and in bench experiments spiking solutions of lipase with glyphosate, glyphosate was not detected by HPLC MSMS. The glyphosate chemically bonded to the lipase protein enzyme making it non-detectable. However, it could be detected by ELISA. LSC (liquid scintillation counting) will also detect the 13-C, 14-C radio labeled glyphosate in this experiment. Glyphosate cannot be detected if it is liganded to proteins it must be released first.

Such ligation and integration has serious biological consequence especially to human health. Lipase is not only secreted by the pancreas, but it also found in the cells. Precise ligation and modeling of glyphosate with lipase is yet to be determined by x-ray crystallography. Enzyme-glyphosate ligation is real, it happens. In my honest opinion, this has far reaching consequences to both human and animal health. Interference with enzymes also leads to disruption of bacterial homeostasis and the bimolecular products they produce which are essential to the host. Interference also induces microbial pathogenic overgrowth and alters substrate availability for healthy bacterial specie colonization. I also found glyphosate conjugated with bile acids which work in concert with lipase in the digestion of fats.

Glyphosate disruption and inhibition of bile and digestive enzymes leads to malabsorption and serious health consequences. One example: Glyphosate's disruption and inhibition of Lipase defeats Beta-cell secretion of insulin. Glucose induces lipolysis and Glyphosate's inhibition of lipase limits lipolysis and diacylglycerol lipase activity in the pancreatic islets. Monsanto found problems with the pancreatic islet tumors as well as structural destruction of this and other glands and organs related to glyphosate integration with structural proteins.

From my lab experiments with Lipase and Glyphosate using HPLC MSMS detection it appears that glyphosate irreversibly inhibits lipase. So, glyphosate would necessarily disrupt lipase's regulatory role in beta-cell stimulus secretion, *see Glyphosate VI*.
Lipase participates in cell signaling, inflammation and metabolism. Pancreatic lipase is the catalyst for the hydrolysis of dietary lipids which include fats, oils and triglycerides. Triglyceride triester is metabolized for utilization as glucose and three fatty acids.

Glyphosate integration with lipase inhibits its function which could induce excessive bioaccumulation of fatty material in the blood vessels, gut, liver, spleen and other organs as well as mimic lysosomal acid lipase deficiency. It would also allow for an increase in triglycerides in the blood and lead to numerous disease cascades including malabsorption, fatty liver disease, jaundice, failure to thrive in infants, calcification of the adrenal gland, anaemia, hypercholsteremia, biliary dysfunction, decreased HDL, increases in LDL, blood clots, fat enlarged hepatocytes, liver fibrosis and failure.

I have found glyphosate in digestive pepsin in the lab. Glyphosate integration with the digestive pepsin is also not without consequence and has serious implications with acid reflux and lung disease among others. Monsanto pathologists found that glyphosate caused digestive inflammation and symptoms in the laboratory rats similar to COPD. I would note our early papers on glyphosate and gastrointestinal disease as well as this article:

ROLE OF PEPSIN IN REFLUX, LUNG DISEASE

"Although acid is indeed one of the culprits in cases of gastroesophageal reflux disease (GERD), a growing body of evidence suggests that pepsin, an enzyme, is the substance that causes the most damage when the

reflux extends beyond the upper esophagus and reaches the pharynx, larynx and lungs. Once present in sufficient amounts, studies have shown, pepsin can cause significant damage by adhering to laryngeal cells and breaking down proteins, among other injurious effects (published online November 10, 2011. Int J Otolaryngol. doi: 10.1155/2012/646901). Thus, it's not surprising that pepsin has been linked to serious lung disease, including acute exacerbations of idiopathic pulmonary fibrosis (Eur Respir J. 2012;39:352-358)." Otolaryngologists Research Role of Pepsin in Reflux, Lung Disease - http://www.enttoday.org/article/otolaryngologists-research-role-of-pepsin-in-reflux-lung-disease/

The fact that glyphosate bioaccumulates and integrates with human enzymes and structural proteins in man and other animals, should be reason enough to ban this substance completely. There should be no glyphosate or glufosinate in the food supply nor in drinking water, air or soil. Glyphosate is a synthetic amino acid that should have no place in biology.

The innate immune system (IIS), part of our overall immune system though not providing long-term immunity, responds to pathogens and recruits the immune cells to infection sites by cytokines or small proteins which participate in cell signaling i.e. autocrine endocrine, paracrine. Cytokines are produced in a wide variety of cell types including fibrocyte / fibroblasts which promote wound healing. So biological disruptions by glyphosate may directly impact fibrocystic cytokines discussed on the next page of this document.

I received a response letter from the EPA through my US Senator Jeanne Shaheen's office denying my assertions that glyphosate was an antibiotic. I alerted them and the rest of the planet to a Monsanto US patent to this regard. The agency stated it was not registered with the FDA as an antibiotic and so, therefore it was not an antibiotic. The agencies statements in that letter to my US Senator were irrational and false.

Additionally, in another letter of response to me, sent to my US Senator, you told us that glyphosate dd not function at the molecular level. That statement to the Senator and I was also false, because any biochemist knows glyphosate functions at the molecular level. I warned the agency about both glyphosate and glufosinate causing problems in animal

biology at the molecular level, but the agency chose to continue to support Monsanto's unfounded claims of product safety.

In a letter sent by me to the EPA and USDA dated September 24, 2012 a copy of which was also sent to US Senator Jeanne Shaheen of New Hampshire, I wrote and stated:

"*Glyphosate destroys and or alters the bacteria (Flora) of the gut and colon, disrupting the biosynthesis of cyclical amino acids, as in plants. This is a sobering detail that Monsanto and the EPA missed upon registering this material, probably due to lack of knowledge about bacterial function. Monsanto originally said that glyphosate was safe because the material works through the Shikimate Pathway which plants have and humans and animals do not."*

"Plants are killed by glyphosate effectively, by stopping the plant from producing three cyclical amino acids which are necessary for life. Amino acids are the building blocks of life. The three cyclical amino acids are tryptophan, tyrosine and phenylalanine. Lack of any one of these amino acids precedes chronic disease. The interference with amino acids at the molecular level is disturbing, as many necessary and essential biological processes are disrupted."

"One of the many functions of bacteria in the gut and colon of humans and other animals is the production of cyclical amino acids. Our bodies cannot make them and must receive them from dietary protein or by the assistance of commensal bacteria. This symbiotic relationship was not known in 1976 and thus was not considered in herbicide registration. However, that is not the case today. All herbicides, fungicides, pesticides and other chemicals used in food should and must be evaluated for their effects on commensal bacteria which are necessary for our overall health and longevity."

"Glyphosate and its metabolite AMPA also act as signaling molecules. Their effect on amino acid and protein biosynthesis leads to a cascade of disease. Based on the disruption of amino acids, the diseases and increases seen in disease would include but are not limited to autism and other autistic spectrum disorders (ASD), Alzheimer's, glycogen storage diseases, obesity, diabetes, celiac disease, acid reflux and other digestive disorders, birth defects, infertility, sterility, sexual dysfunction, vitamin D

deficiency, lack of folate and other B vitamins, chelation of other necessary minerals and more."

In that letter, I warned the agency that glyphosate affects microbiota and enzymes in all animals. Monsanto's assumption and statements against my assertions in this regard are inherently false as glyphosate was found by Samsel in 2016 to inhibit human digestive enzymes and others found in animals and humans. Glyphosate is a *protease inhibitor* i.e. digestive enzymes etc. Such disruption of human enzymes is well known to lead to a host of modern diseases.

It was I who first made the biochemical connections at the molecular level, of glyphosate and glufosinate to the rise in all modern diseases and now numerous research studies by colleagues at universities around the planet now back up my elucidations.

I remind you, Monsanto found significant tissue damage to all glands and organs in their 2-year long-term studies of glyphosate in mice and rats. Tissue damage stimulates the production of fibrocytes. Glyphosate reaches the end of the line in the capillaries in the extra cellular matrix (ECM) where it is escorted *one molecule at a time* into the cell where it participates in protein synthesis and excretion by the cell.

Fibroblasts also produce the structural proteins i.e. the collagens, elastin, glycosaminoglycans and the glycoproteins of the ECM … so glyphosate is along for the ride even bridging assembling strands of proteins affecting shape folding and function. The synthetic amino acid Glyphosate should not be part of any biology.

Also fibrocytes and fibroblasts are differing states of the same cell the fibroblasts of which are involved in immune regulation via TAF-derived elements of the ECM and modulators. These ECM components like TSP-1 are associated at the sites of chronic inflammation and **carcinomas**. This is where glyphosate causes many funky cancers, as its association with the fibroblasts.

I have published results of lab analysis and experiments on glyphosate integration with structural proteins, as well as proteinaceous enzymes. Glyphosate chemically bonds and integrates with proteins causing misfolding and malfunction. Protein function involves *ligation* of ions and both small and large molecules through random collisions. The ligation

involves the wrapping of the substrate around the protein which changes its shape and blocks its ability to function. This is one of the many ways glyphosate functions in biology.

In March 2017 another peer-reviewed paper was published: Glyphosate pathways to modern diseases VI: Prions, amyloidosis and autoimmune neurological diseases. The paper notes that based on Monsanto's own studies and data that glyphosate bioaccumulates in all cells and tissues including eggs and the milk of all animals fed a diet of glyphosate residues. The data developed by Samsel in this paper also supports these conclusions, but goes beyond Monsanto's findings. Bioaccumulation information extracted from Monsanto sealed studies is contained on page 14 and 15 of that paper.

I have analyzed tissues from horses and humans as well as, the tissues of pigs and cattle from the food supply obtained at supermarkets and found all tissues ubiquitously contaminated with glyphosate. I found glyphosate in gelatins, collagens, keratins as well as eggs and semen raising the issue of infertility. I have found particularly high levels of glyphosate in the bones of animals, as did Monsanto in chronic animal feeding studies.

I have recently followed glyphosate from horse feed into the keratin of the hooves of the animal at 52-63 ppb glyphosate. I have identified structural defects in the keratin protein found in horses with collapsing hooves. These animals eating contaminated feed have glyphosate bioaccumulating in all tissues. I have found it circulating in their blood, their urine, manure and keratin in the hooves. The only way glyphosate can become part of the protein keratin is by cell secretion and integration with the protein hence the defective proteins. Structural proteins including Intermediate Filaments (IFs) which participate in signaling also control *apoptosis.*

I am finding glyphosate in the keratin of the defective fingernails and toenails of humans and in one patient with up to 15 ppb glyphosate in these tissues. This person suffers debilitating scleroderma and I have attached a picture of these finger nails at the end of this document. I have also found 9-10 ppb as an integral part of the teeth of children some now deceased. Recently, I found glyphosate in the biopsied sample of human tissue of the spinal disc of a 40 year old man from Germany

suffering from age related spinal degeneration. The defective structural proteins of the spinal disc contained 2.40 ppb of glyphosate.

The synthetic amino acid Glyphosate is a structural analog of our canonical amino acid glycine. It is a relatively small molecule which can travel anywhere glycine travels. It bonds and integrates with structural proteins as well as many enzymes including the digestive enzymes of man and other animals. This causes malabsorption and intestinal issues and cascades of disease consequence. Inhibiting our enzymes is not without significant consequence as is glyphosate bioaccumulation as part of our structural proteins. Based on this alone glyphosate should be banned. No chemical should be allowed in food or water that disrupts enzymology, none.

In closing, I would remind agency members of the letter written to you by a former employee of the agency, the late Marion Copley was also aware of some of my elucidations. In that letter shortly before death by cancer, stated in part:

“Since I left the Agency with cancer, I have studied the tumor process extensively and I have some mechanism comments which may be very valuable to CARC based on my decades of pathology experience.”

“Glyphosate was originally designed as a chelating agent and I strongly believe that is the identical process involved in its tumor formation, which is highly supported by the literature.
-Chelators inhibit apoptosis, the process by which our bodies kill tumor cells -Chelators are endocrine disruptors, involved in tumorigenesis
-Glyphosate induces lymphocyte proliferation
-Glyphosate induces free radical formation
-Chelators inhibit free radical scavenging enzymes requiring Zn, Mn or Cu for activity (i.e. SODs)
-Chelators bind zinc, necessary for immune system function
-Glyphosate is genotoxic, a key cancer mechanism
-Chelators inhibit DNA repair enzymes requiring metal cofactors
-Chelators bind Ca, Zn, Mg, etc to make foods deficient for these essential nutrients
-Chelators bind calcium necessary for calcineurin mediated immune response
-Chelators often damage the kidneys or pancreas, as glyphosate does, a mechanism to tumor formation -Kidney/pancreas damage can lead to

clinical chemistry changes to favor tumor growth -Glyphosate kills bacteria in the gut and the gastrointestinal system is 80% of the immune system
-Chelators suppress the immune system making the body susceptible to tumors"

"Previously, CARC concluded that glyphosate was a "possible human carcinogen". The kidney pathology in the animal studies would lead to tumors with other mechanisms listed above. Any one of these mechanisms alone listed can cause tumors, but glyphosate causes all of them simultaneously. It is essentially certain that glyphosate causes cancer. With all of the evidence listed above, the CARC category should be changed to "probable human carcinogen". Blood cells are most exposed to chelators, if any study shows proliferation of lymphocytes, then that is confirmatory that glyphosate is a carcinogen."
"

…. "For once do the right thing and don't make decisions based on how it affects your bonus." …"I have cancer and I don't want these serious issues in MED to go unaddressed before I go to my grave. I have done my duty." ~ Marion Copley

I concur with and in memory of the late Marion Copley do ask this agency not to re-approve the registration of Glyphosate. It is not a building block of life, but rather antithetical to that process and to all living things on our planet.

We are but one biosphere, what affects one affects all. ~ Anthony Samsel

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"In the past the world suffered grievously from lack of knowledge, today it suffers from its rejection." ~ Dr. Arthur D. Little

(1) Samsel, Anthony Malignant Haemangio-endotheliomas found in mice administered glyphosate

(2) EPA (1985b). EPA Reg.#: 524–308; Roundup; glyphosate; pathology report on additional kidney sections.
Document No. 004855

(3) EPA (1983). Review of Knezevich A, Hogan G (1983). A chronic feeding study of glyphosate (Roundup Technical)
in mice: Project No. 77–2061: BDN-77- 420. Final Report. MRID 00130406. Washington (DC): United States Environmental Protection Agency.

(4) EPA (1985a). Glyphosate; EPA Reg.#: 524–308; Mouse oncogenicity study. Document No. 004370. Washington (DC): Office of Pesticides and Toxic Substances, United States Environmental Protection Agency.

(5) Monsanto's unpublished study #BDN-77420 "A Chronic feeding study of Glyphosate (Roundup Technical) in mice" Knezevich and Hogan (1983)

(6) Samsel & Seneff, Glyphosate, pathways to modern diseases IV: cancer and related pathologies
January 2015 Journal of Biological Physics and Chemistry 15(3) 121-159DOI10.4024/11SA15R.jbpc.15.03 https://www.researchgate.net/publication/283490944_Glyphosate_pathways_to_modern_diseases_IV_cancer_and_related_pathologies

(7) https://rarediseases.info.nih.gov/diseases/6557/hemangioendothelioma

(8) https://www.chla.org/hemangiomas

(9) https://www.stjude.org/disease/epithelioid-hemangioendothelioma.html

(10) Konishi Y, Ikeda T, Yoshimura H, Kawabata A, Mikami R. Carcinogenic effect of N-bis(2 hydroxypropyl)nitrosamine by a single administration in rats. Cancer Lett. 1979 Feb; 6(2):115-9.

(11) Konishi, Y & Kondo, H & Inui, S & Denda, A & Ikeda, T & Kojima, K. (1978). Organotropic effect of N-bis(2-hydroxypropyl)nitrosamine: Production of lung and liver tumors by its oral administration in mice. Gann = Gan. 69. 77-84.

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https://www.researchgate.net/publication/283490944_Glyphosate_pathways_to_modern_diseases_IV_cancer_and_related_pathologies

https://www.researchgate.net/publication/305318376_Glyphosate_pathways_to_modern_diseases_V_Amino_acid_analogue_of_glycine_in_diverse_proteins

https://www.researchgate.net/publication/316601847_Glyphosate_pathways_to_modern_diseases_VI_Prions_amyloidoses_and_autoimmune_neurological_diseases

https://www.researchgate.net/publication/323176357_Malignant_Haemangio-endotheliomas_found_in_mice_administered_glyphosate

https://www.researchgate.net/publication/316831330_Glyphosate_Malignant_Lymphomas_in_female_rats_administered_glyphosate_in_the_diet_Extracted_data_1981

PLEASE SEE LYMPHOMA AND HEMANGIOENDOTHELIOMA DATA BELOW

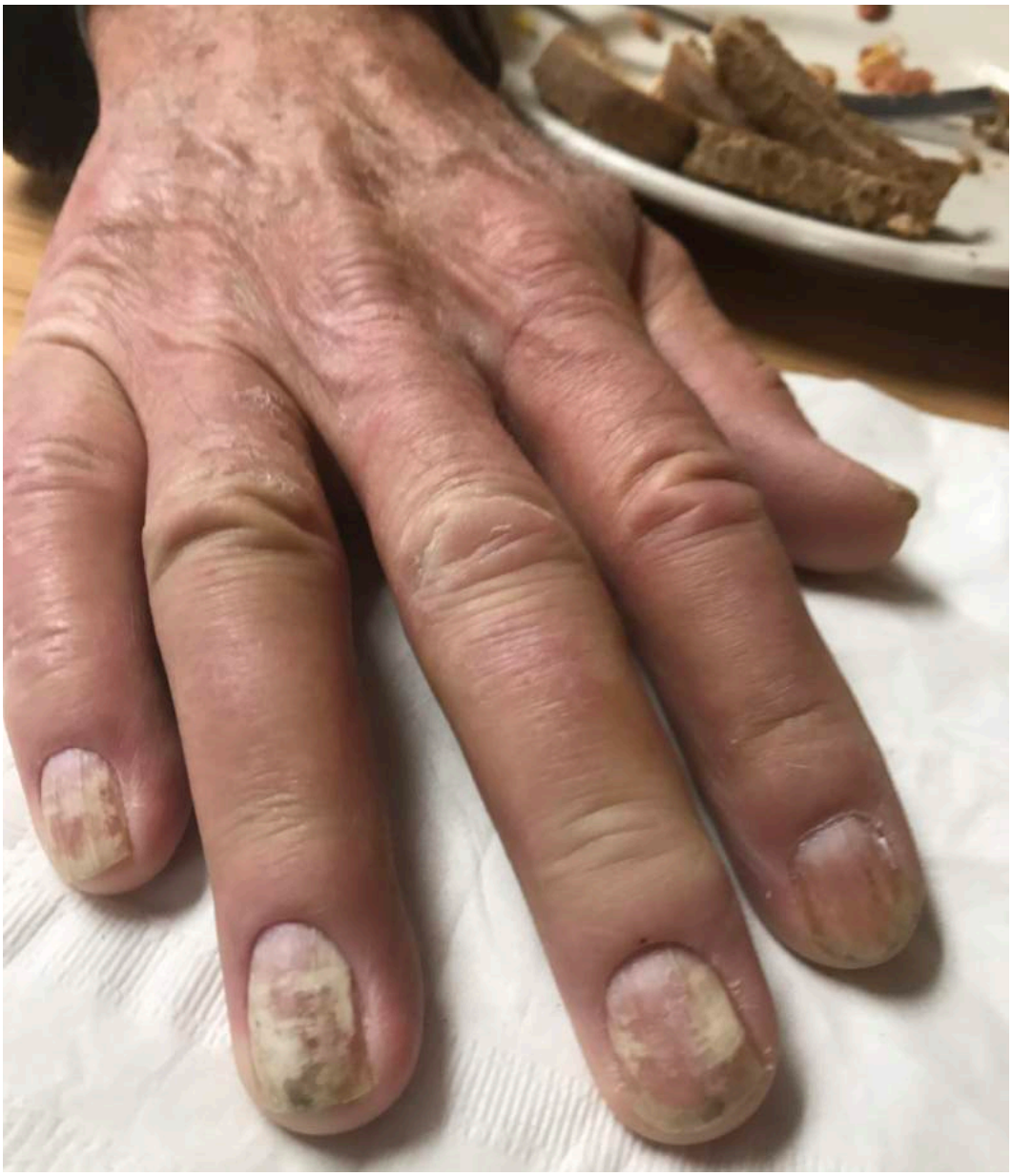
Malignant Lymphomas found in female rats administered glyphosate in the diet. Data extracted from Monsanto 2-year study
Lankas & Hogan (1981)

Glyphosate Dose mg/kg/day number affected / number of animals	0 control	5 treated---->	10	30
BRAIN	0/50	0/50	0/50	1/50 (2%)
SPINE	0/50	0/50	0/50	1/50 (2%)
HEART	0/49	1/50 (2%)	0/50	1/50 (2%)
LUNG	0/49	1/50 (2%)	0/49	1/50 (2%)
LIVER	0/50	0/50	1/50 (2%)	2/50 (4%)
THYMUS	0/25	0/32	1/37 (3%)	1/34 (3%)
SPLEEN	0/50	0/50	1/50 (2%)	2/50 (4%)
STOMACH	0/50	0/50	0/50	1/50 (2%)
BONE MARROW	0/46	0/44	1/46 (2%)	1/45 (2%)
ADRENAL GLAND	0/50	0/50	0/50	1/49 (2%)
HARDERIAN GLAND	0/47	0/45	0/47	1/44 (2%)
LYMPH NODE MESENTERIC	0/42	0/39	0/48	1/47 (2%)
LYMPH NODE MANDIBULAR	0/2	0/3	0/6	1/6 (17%)
LYMPH NODE MEDIASTINAL	0/33	0/29	1/37 (3%)	2/30 (7%)

Malignant Haemangio-endotheliomas found in mice administered glyphosate

Data extracted from: "A chronic feeding study of Glyphsaote (Rounup technical acid) in mice"
Knezevich & Hogan (1983)unpblished study #BDN-77420 Bio/Dynamics for Monsanto

Glyphosate Dose ppm/day number affected / number of animals	0 control	1000 treated---->	5000	30,000
FEMALE MICE		HAEMANGIO-ENDOTHELIOMA		
LIVER			1/49 MG 2% 2/49 MS 4%	
SPLEEN	1/50 MG 2%		2/49 MG	1/49 MG 2% 1/49 MS 2%
UTERUS				1/50 MG 2%
MESENTERIC LYMPH NODES				1/49 MS 2%
		HAEMANGIOMA		
UTERUS		1/48 MS 2%		1/49 MG 2%
MALE MICE		HAEMANGIO-ENDOTHELIOMA		
SPLEEN			1/50 MG 2%	
		HAEMANGIOMA		
MESENTERY		1/2 MS 50%		
TOTALS Haemangio-endothelioma	1	2 (Haemangiomas)	6	5
MG = Malignant MS= Metastatic				



A scleroderma patient's defective fingernails the keratin protein of which contained 15.08 ppb Glyphosate

Some of the cat and dog foods analyzed in the lab by HPLC MSMS

In 2014 Samsel and Seneff found 170 ppb of Glyphosate in Enfamil ProSobee Infant Formula

"Glyphosate, Pathways to Modern Disease III: Manganese, Neurological Disease and Associated Pathologies"-Samsel and Seneff 2015

Glyphosate and AMPA in Soybeans USDA Pesticide Data Reported 2012

Slide © Anthony Samsel

	% Samples with detections	Number analyzed	Number with detections	Range ppm	Mean ppm	EPA tolerance
Glyphosate	90.3	300	271	0.26 -18.5	1.973	20.0
AMPA	95.7	300	287	0.26 -20	2.279	20.0

How many children will we continue to harm with soy based infant formulas ?