EXHIBIT 1

TCAS

Toxicology Consultants & Assessment Specialists, **LLC**
6450 Pine Avenue, Sanibel, FL 33957
29 Fennell Street, Skaneateles, NY 13152
(239) 472-2436 [FL] (315) 685-2345 [NY] (800) 308-0080 U.S./CA
E-mail: drsawyer@experttoxicologist.com & Website: experttoxicologist.com

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January 22, 2021

Ken Moll, Esq.
Moll Law Group, PC
22 W. Washington St, 15th Floor
Chicago, IL 60602

Re: Cervantes v. Monsanto

Dear Attorney Moll:

Per your request with regard to this matter, I have reviewed the complete list of pertinent documents as compiled in Appendix A. Based upon the information provided and the application of generally-accepted toxicological methodology and referenced sources as cited herein, I have stated my opinions in this matter to reasonable toxicological certainty.

Note: Headings containing (**) denote sections recently added to the main report body.

Contents

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1. Introduction

This section outlines the report objectives and provides an overview of the methodology employed to assess the historical exposures sustained by the plaintiff in the current matter, Gerard Francis Cervantes, to Monsanto's Roundup® product. Mr. Cervantes was diagnosed with diffuse large B-cell lymphoma (non-Hodgkin's lymphoma or "NHL") allegedly as a result of repeated exposures to this product. Section 2 of this report assesses medical history, familial malignancies, history of tobacco, alcohol and drug use, dose/exposure-day calculations, specific causation toxicological confounding factors (including differential diagnoses of potential chemical, pharmaceutical and radiological exposures) and other potential confounding toxic etiological factors.

Overview of Toxicological Methodology

Throughout this assessment, I have applied the generally-accepted Bradford Hill and weight-of-evidence (WOE) methodology using peer-reviewed toxicological studies. Frequency and duration of exposure, circumstances of application, personal protective equipment (PPE), environmental considerations and other pertinent factors have been compiled and referenced to human toxicological and epidemiological studies. Potential exposures to other chemical and/or radiological substances (including use of pesticides, paint, paint solvents, petroleum products, benzene, other home gardening/landscape chemicals, occupational exposures, etc.) have also been assessed as potential toxicological factors with respect to NHL causation. Smoking history (pack-years and cessation duration, if any), family medical history, alcohol consumption, drugs-of-abuse, prior diagnoses with respect to any immuno-suppressive diseases, prior malignancies (if any) and any prior pharmacological intervention which may present increased toxicological risks of NHL (such as cyclophosphamide, cyclosporin, etc.) have also been assessed. Additionally, the NHL diagnosis and pathology records have been referenced with respect to subtypes or other significant findings. Supporting toxicological studies, literature citations, footnote references to testimony and other references relied on are itemized in Appendix A and footnoted throughout as appropriate.

Objectives

One of the primary objectives of this toxicological assessment is to arrive at a scientifically accurate and reliable time-weighted exposure dose for Mr. Cervantes based on 8-hour time-weighted *exposure-days* (for comparison with the human epidemiological studies of applicators). My toxicological assessment is also designed to evaluate and weigh all other

potential contributing toxicological factors and assess the latency period from initial exposure to the time of Mr. Cervantes' diagnosis.

Additionally, based on the available objective evidence and state-of-the-art scientific literature, I will opine whether Mr. Cervantes' alleged cumulative Roundup® dosage was a substantial contributing factor to the development of his NHL.

Mr. Cervantes' exposures have been assessed based on historical information received through review of personal fact sheets, deposition, photographs and direct interview pertaining to his exposure events, circumstances and details. From this information, a cumulative time-weighted dose for Mr. Cervantes has been calculated using simple additive mathematical methodology in units of 8-hour time-weighted "exposure days" for comparison to the threshold values in the human epidemiological studies of applicators that revealed statistically-significant elevated odds ratios (ORs).

Although specific mg/kg-body weight calculations were not performed using the generally-accepted "predicted operator exposure model" (POEM), the POEM has been used with respect to dose and exposure factor intensity such as gloves vs. no gloves, type of nozzle (aerosol vs. CDA[1]), professional applicator exposures vs. home users, etc. It should be noted that dose measurements assessed using the POEM methodology in units of mg/kg/day are of limited use and are gauged against the "acceptable operator exposure limit" (AOEL) which is designed for protection against **non-cancer endpoints** (i.e., reproductive toxicity among rodents). The AOEL does not assess human cancer risk.

The POEM methodology has been peer-reviewed, generally-accepted, used internationally and tested with a known rate of error as published within the seven studies footnoted below.[2]

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[1] Controlled droplet application.

[2] Abukari, Wumbei, "Pesticides Applicator Exposure Assessment: A Comparison between Modeling and Actual Measurement," 2015, Journal of Environment and Earth Science ISSN 2224-3216 (Paper) ISSN 2225-0948 (Online) Vol.5, No.11.

U.K. Health and Safety Executive, HSE, "Operator Exposure," 2016, Data requirements handbook, Retrieved from: http://www.hse.gov.uk/pesticides/topics/pesticide-approvals/pesticides-registration/data-requirements-handbook/operator-exposure.htm

"Operator exposure assessment for MON 2139 UK – Case" MONGLY06509236

"UK POEM calculations in preparation of meeting Spanish competent authorities." MONGLY01275627

Lawson, A., et al., "Three Methods to Assess Levels of Farmers' Exposure to Pesticides in the Urban and Peri-urban Areas of Northern Benin," 2017, Tunisian Plant Protection Journal, Vol.12, pp. 91–108.

Hence, this toxicological assessment has four fundamental objectives: (1) to arrive at a scientifically-reliable exposure dose estimation for Mr. Cervantes (*in units of 8-hour time-weighted exposure days*) based upon the available objective evidence, (2) to assess the potential of confounding toxicological risk factors contributing to his NHL onset, (3) to provide a general causation assessment of personal protective gear (PPE), product formulation, toxicological factors such as absorption, distribution, metabolism and excretion (ADME) and mechanism of action of Roundup and (4) to render a scientifically-supported and reliable opinion as to whether Mr. Cervantes' Roundup exposures (dose) were sufficiently above the thresholds within the peer-reviewed studies to substantially contribute to the development of his NHL.

B. Plaintiff Background Summary

Introduction

Gerard Francis Cervantes was born on [redacted] in Aurora, Illinois and was 60 years old at the time of his deposition in the current matter.[3] He attended Johnson Elementary School and Simmons Middle School; he subsequently graduated from East Aurora High School in 1977.[4] He served in the military from 1977 to 1979 in the U.S. Marine Corps.[5] He lived with his parents for a time, then was married and lived in Aurora from approximately 1982 to 1996, at which time he relocated to Sugar Grove, IL. He continues to reside there to the present day.

After his two years in the Marine Corps, Mr. Cervantes began working for a local gas company, initially as a welder and later as a "lead person." He worked his way through the ranks and was eventually promoted to a managerial position in the company. Mr. Cervantes also started his own business in the late 1990's in which he engaged in lawn maintenance activities. It was during this interval that his primary Roundup® exposures occurred.

Illyassou, K., et al., "Risk Assessment for Small Farmers Exposed to Plant Protection Products in the Niger River Valley," 2017, Comm. Appl. Biol. Sci.

EPA, "Risk Assessment Methodology for Hazardous Substances: How to assess the risk, cost and benefit of new hazardous substances for use in New Zealand," 2018, Environmental Protection Authority.

[3] Deposition of Gerard F. Cervantes, June 23, 2020, Chicago, Illinois.

[4] Id., pp. 9-10.

[5] Id., p. 79 and interview 1/7/2021.

Employment History

In late 1979, Mr. Cervantes began working for Northern Illinois Gas Company (now called Nicor Gas). He started as a meter reader and was later promoted to maintaining gas lines. He subsequently became a certified pipeline welder and was promoted to lead manager responsible for the crew, machine operator and the work performed.[6] Eventually, in 1992, he was given the opportunity to work in the company headquarters in a management role in the safety and training department. After 3 years, he returned by choice to his former position as a lead in the street department supervising a team.[7] He left the company in 2009 on partial disability owing to his cancer diagnosis.[8]

Mr. Cervantes was subsequently named as a plaintiff in a 2006 class action lawsuit against Nicor Gas seeking compensation for his NHL based upon a belief that his job had resulted in exposures which led to cancer. This belief was due to the absence of a backflow valve in the company boiler which was thought to contain chemicals that had contaminated the drinking water. The case was subsequently dismissed; Mr. Cervantes played no active role in the proceedings.[9]

In 1998, Mr. Cervantes started his own lawn care business, first named "ASC Lawn Care" and then "Dr. J. Lawn Care." Mr. Cervantes testified that, "the basic scope would be cutting grass, trimming bushes, putting down mulch, what we call bed edging and at that initial time, maintaining weeds, weed control. We started out as residential and as we grew, incorporated commercial properties also." His regular work schedule ran from 20 to 40 hours per week and he is still engaged in his lawn care work. Mr. Cervantes applied Roundup® in his lawn care business from 1998 through 2004 when he ceased to use it following his NHL diagnosis.[10]

Personal Medical History

Mr. Cervantes had a tonsillectomy at approximately age 9. As is the case with most adults, he experienced occasional flu viruses and at one point was diagnosed with a mild case of shingles. No other significant diseases, illnesses or injuries were reported. He testified

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[6] Deposition of Gerard F. Cervantes, June 23, 2020, p. 31.

[7] Id., p. 37.

[8] Id., pp. 29-30.

[9] Id., pp. 11-12.

[10] Id., pp. 60-64.

that he had not been involved in any Workers' Compensation matters and maintained his good health throughout the tenure of his employment.

At one point, Mr. Cervantes was treated for an atrial fibrillation (A-fib) condition via a corrective ablation procedure. This was a completely successful process. He has experienced sleep apnea but ceased using a CPAP device upon losing some weight which seemingly corrected his snoring and breathing issues.[11]

Mr. Cervantes indicated in his Plaintiff Fact Sheet that his mother was diagnosed with cancer in 1998. Mr. Cervantes has not been diagnosed with diabetes, obesity, auto-immune diseases (Crohn's disease, ulcerative colitis or HIV), Epstein Barr, ulcers, Celiac disease, Hepatitis C, eczema, lupus or rheumatoid arthritis.[12]

Mr. Cervantes stated that he has enjoyed a lifetime of good health prior to the NHL. He reports that all of his children are presently in good health. He has 13 siblings, one of whom has contracted colon cancer. His father was also extremely healthy and lived to 90 years of age. Mr. Cervantes says he "died of old age."[13] When questioned about his personal health by defendant's attorney, Mr. Cervantes responded:

Q. How would you describe your health prior to your NHL diagnosis?

A. Very good. Prior to getting sick, other than you get a common cold there once in a while, you catch a flu because I worked outside all year around. I've never had a broken bone. Other than my tonsils, been good. And at one time I went ten years without missing a day's work calling in sick.[14]

Mr. Cervantes testified that he has not previously been exposed to radiation other than post-diagnostic chemotherapy. He has no documented genetic predisposition to cancer and was not prescribed immunosuppressive medications prior to his NHL diagnosis. He was administered a stem cell transplant by his oncologist following his NHL diagnosis.[15]

NHL Diagnosis and Pathology

In 2004, Mr. Cervantes began experiencing night sweats, fatigue, bone and joint aches and a variety of other symptoms. In September 2004 (at the age of 45), he presented to

[11] Id., p. 178.
[12] Plaintiff Fact Sheet, Gerard F. Cervantes, dated August 30, 2019.
[13] Deposition of Gerard F. Cervantes, June 23, 2020, pp. 192-193.
[14] Id., p. 180.
[15] Id., p. 174.

Advocate Medical Group in Aurora, Illinois. He underwent a liver needle biopsy and was given a variety of related tests. On September 26, 2004, the final pathology confirmed *diffuse large B-cell lymphoma*.

At the time of Mr. Cervantes' NHL diagnosis, he was deemed to be in "Stage IV" of the disease progression. The cancer was successfully put into remission by his first round of treatment. However, after several years of comparative good health, Mr. Cervantes again began experiencing night sweats, fatigue, bone and joint aches and other symptoms.

Upon presenting to his physician in 2009 and running appropriate tests, he was informed his NHL had reappeared and had returned to "Stage I" progression. He was subsequently treated with two years of aggressive chemotherapy which concluded in May 2011.[16] Altogether, Mr. Cervantes received 6 cycles of R-CHOP treatment and was also given an autologous stem cell transplant.

His cumulative treatments were both physically and emotionally demanding, and he so noted this fact in deposition.[17] He was prescribed Rituxan and continues to attend periodic oncological visits to monitor his condition and progress.

A subsequent pathology report stated, *"Liver needle biopsy: liver parenchyma with portal involvement of B-cell lymphoma, large cell type. The diagnosis was made in conjunction with Mayo Clinic (HR04-51484). Tumor cells are positive for CD20 and CD45 and negative for CD3, CD15 and CD30 by outside immunostains."*

History of Tobacco, Alcohol and Drug Use

Mr. Cervantes is a lifetime non-smoker; He has never smoked cigars, pipes or vapes. He has never used any tobacco products. He has never used chewing tobacco. He testified that he has never used illegal drugs of any kind. His alcohol consumption is extremely minimal. His characterization was, "Slim. A case of beer would last me, if I drank it myself, probably five or six months." He has never consumed coffee.[18]

[16] Deposition of Gerard F. Cervantes, pp. 206-210.

[17] Id., pp. 211-212.

[18] Id., p. 189.

Exposure Factors

Mr. Cervantes testified that while engaged in the work for his own company, ASC Lawn Care, he used only Roundup® and applied no other chemicals, fertilizers, weed control products, insecticides or pesticides in his work. He occasionally installed mulch as needed by the job requirements, but no other chemical substances were applied.[19]

Mr. Cervantes used Roundup® for both his occupational and residential spraying activities. His residential use of Roundup® commenced in approximately 1982 at [redacted] He testified that this residential use was episodic and limited to spot-spraying, generally prior to pulling weeds, and to kill weeds around the house. He also sprayed cracks in concrete and his driveway.[20]

Mr. Cervantes was asked to estimate the areas sprayed in his residential properties. He testified that in his first home, the area sprayed was approximately [120+160] = 280 sq. ft. In his second home on New Merrill Road, he estimated the area treated was much larger at approximately [600+280+30+40+200] = 1,150 sq. ft (est.).

None of the properties at which Mr. Cervantes applied Roundup® occupationally were agricultural locations. His primary clients consisted of residential customers, churches, nursing homes, subdivisions, etc. Most of his spray activities were "spot-spray" but in some instances, he also treated large open areas.[21]

When conducting Roundup® applications in his lawn care business, Mr. Cervantes used the Roundup® Weed and Grass Killer product on a regular, weekly basis.[22]

With respect to Mr. Cervantes' commercial applications of Roundup, he stated, "Initially, just small residential yards to get started and then going forward and growing. I'd say at my busiest, we had three nursing homes, two large churches and two good size subdivisions that we would maintain their common areas, and about 20 residential. He also responded to the question, "And would you use the entire 3 gallons when you sprayed those particular properties?" His answer: "In a day, yes, because I would make, you know, two or three nursing homes in one day."

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[19] Deposition of Gerard F. Cervantes, June 23, 2020, pp. 71-73.
[20] Id., pp. 103-107.
[21] Id., pp. 147-151.
[22] Id., p. 135.

Mr. Cervantes testified that he sprayed his [each][23] clients' properties once per week throughout the season.[24] He estimated as an example that if he sprayed two or three nursing homes in one day, he typically sprayed for 1-1/2 to 2 hours that day using 3 gallons of Roundup.[25]

Mr. Cervantes estimated that he typically sprayed for 1-1/2 to 2 hours during his work day, sometimes more, sometimes less.

Mr. Cervantes testified that he sprayed his clients' properties once per week throughout the season.[26]

When questioned about potential direct contact exposures, Mr. Cervantes could not recall whether he had been exposed to spray drift. However, he recalled that his hands were sometimes wet with liquid Roundup®. He testified:[27]

> **Q.** Did you ever feel Roundup spray or spill on your exposed skin when you applied it?
>
> **A.** There were times when I'm using the sprayer that it felt, my hand, wet and stuff. So, I don't know if the trigger was leaking or something was leaking there.

Mr. Cervantes mixed the concentrated Roundup® on-site and then poured the solution into a backpack sprayer by hand. He occasionally contacted Roundup® on his hands and would sometimes rinse, but only if possible and/or practical; otherwise, he would merely wipe off the concentrate solution and continue on to the next task.[28]

Roundup® Product Used

Mr. Cervantes identified the product he used as *"Roundup® Grass & Weed Killer."* He could not recall a specific product package as he used several different products including both ready-to-use and concentrated versions. "Some of them were gallon sized with the picture of a weed, and others were the concentrated that we would mix ourselves in a 3-gallon I want to say backpack, went on your back and used it to spray."[29] When applying Roundup® residentially, Mr. Cervantes initially used the 1-gallon container with a trigger

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[23] Per my interview with Mr. Cervantes on January 7, 2021.

[24] Deposition of Gerard F. Cervantes, June 23, 2020, pp. 134-135.

[25] Id., p. 137.

[26] Id., pp. 134-135.

[27] Id., p. 157.

[28] Id., pp. 142-143.

[29] Id., p. 97.

nozzle supplied with the product to apply the liquid. He estimated in deposition that he used approximately 2 gallons per year on a residential basis commencing in approximately 1982.[30] He later began using his backpack sprayer. Mr. Cervantes testified that when using Roundup® occupationally, he purchased Roundup® concentrate weekly from April through November, typically 2-3 containers per week (less at the beginning/end of each season, more during peak work periods).[31] Over time, Mr. Cervantes used the concentrate more frequently as it was more comfortable and efficient for him to use his backpack sprayer. Mr. Cervantes did not know the percentage of glyphosate present in the concentrate he applied. He performed PC searches and located labels for the Roundup® products he did use as shown in **Figures 1** and **2**.

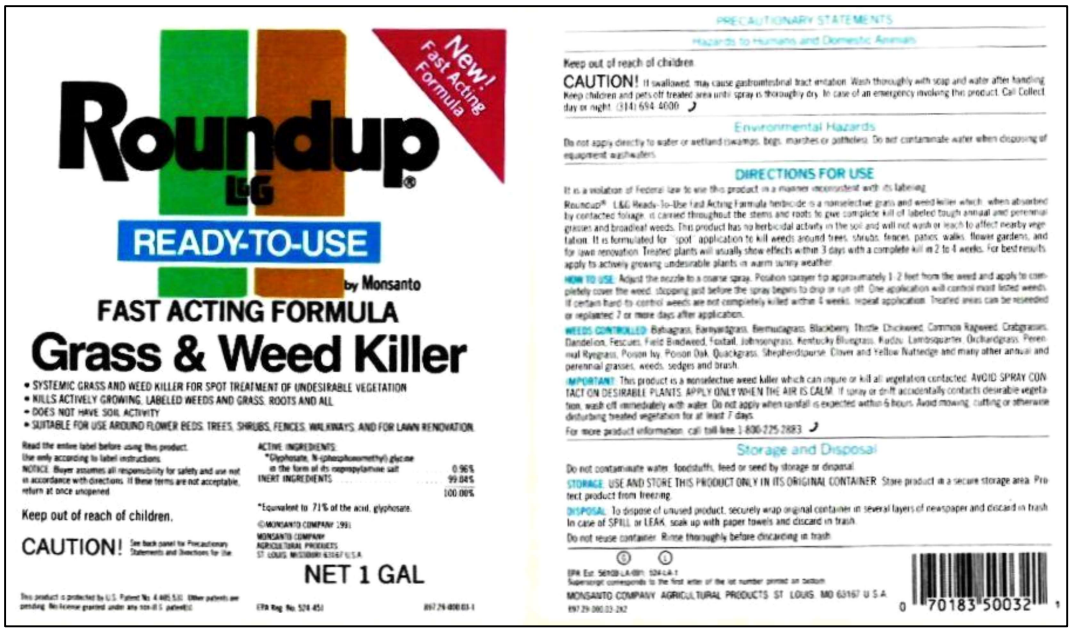
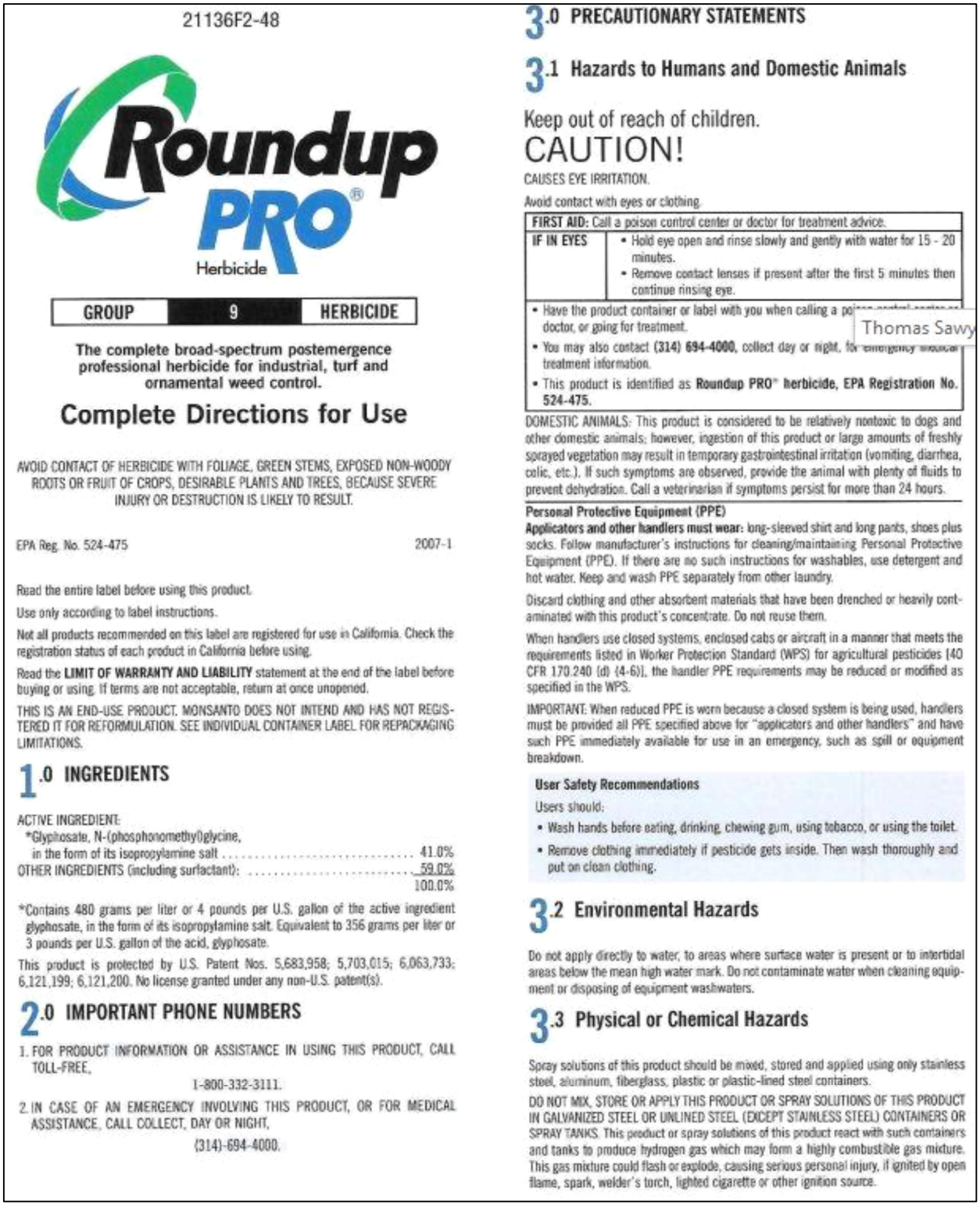


Figure 1: Supplied label of Roundup® product used by Mr. Cervantes

[30] Deposition of Gerard F. Cervantes, June 23, 2020, p. 105.

[31] Id., p. 117.



21136F2-48

Roundup PRO®
Herbicide

GROUP	9	HERBICIDE

The complete broad-spectrum postemergence professional herbicide for industrial, turf and ornamental weed control.

Complete Directions for Use

AVOID CONTACT OF HERBICIDE WITH FOLIAGE, GREEN STEMS, EXPOSED NON-WOODY ROOTS OR FRUIT OF CROPS, DESIRABLE PLANTS AND TREES, BECAUSE SEVERE INJURY OR DESTRUCTION IS LIKELY TO RESULT.

EPA Reg. No. 524-475 2007-1

Read the entire label before using this product.

Use only according to label instructions.

Not all products recommended on this label are registered for use in California. Check the registration status of each product in California before using.

Read the **LIMIT OF WARRANTY AND LIABILITY** statement at the end of the label before buying or using. If terms are not acceptable, return at once unopened.

THIS IS AN END-USE PRODUCT. MONSANTO DOES NOT INTEND AND HAS NOT REGISTERED IT FOR REFORMULATION. SEE INDIVIDUAL CONTAINER LABEL FOR REPACKAGING LIMITATIONS.

1.0 INGREDIENTS

ACTIVE INGREDIENT:	
*Glyphosate, N-(phosphonomethyl)glycine, in the form of its isopropylamine salt	41.0%
OTHER INGREDIENTS (including surfactant):	59.0%
	100.0%

*Contains 480 grams per liter or 4 pounds per U.S. gallon of the active ingredient glyphosate, in the form of its isopropylamine salt. Equivalent to 356 grams per liter or 3 pounds per U.S. gallon of the acid, glyphosate.

This product is protected by U.S. Patent Nos. 5,683,958; 5,703,015; 6,063,733; 6,121,199; 6,121,200. No license granted under any non-U.S. patent(s).

2.0 IMPORTANT PHONE NUMBERS

1. FOR PRODUCT INFORMATION OR ASSISTANCE IN USING THIS PRODUCT, CALL TOLL-FREE,
1-800-332-3111.
2. IN CASE OF AN EMERGENCY INVOLVING THIS PRODUCT, OR FOR MEDICAL ASSISTANCE, CALL COLLECT, DAY OR NIGHT,
(314)-694-4000.

3.0 PRECAUTIONARY STATEMENTS

3.1 Hazards to Humans and Domestic Animals

Keep out of reach of children.

CAUTION!

CAUSES EYE IRRITATION.

Avoid contact with eyes or clothing.

FIRST AID: Call a poison control center or doctor for treatment advice.	
IF IN EYES	• Hold eye open and rinse slowly and gently with water for 15 - 20 minutes. • Remove contact lenses if present after the first 5 minutes then continue rinsing eye.

- Have the product container or label with you when calling a poison control center or doctor, or going for treatment.
- You may also contact **(314) 694-4000**, collect day or night, for emergency medical treatment information.
- This product is identified as **Roundup PRO® herbicide, EPA Registration No. 524-475.**

DOMESTIC ANIMALS: This product is considered to be relatively nontoxic to dogs and other domestic animals; however, ingestion of this product or large amounts of freshly sprayed vegetation may result in temporary gastrointestinal irritation (vomiting, diarrhea, colic, etc.). If such symptoms are observed, provide the animal with plenty of fluids to prevent dehydration. Call a veterinarian if symptoms persist for more than 24 hours.

Personal Protective Equipment (PPE)

Applicators and other handlers must wear: long-sleeved shirt and long pants, shoes plus socks. Follow manufacturer's instructions for cleaning/maintaining Personal Protective Equipment (PPE). If there are no such instructions for washables, use detergent and hot water. Keep and wash PPE separately from other laundry.

Discard clothing and other absorbent materials that have been drenched or heavily contaminated with this product's concentrate. Do not reuse them.

When handlers use closed systems, enclosed cabs or aircraft in a manner that meets the requirements listed in Worker Protection Standard (WPS) for agricultural pesticides [40 CFR 170.240 (d) (4-6)], the handler PPE requirements may be reduced or modified as specified in the WPS.

IMPORTANT: When reduced PPE is worn because a closed system is being used, handlers must be provided all PPE specified above for "applicators and other handlers" and have such PPE immediately available for use in an emergency, such as spill or equipment breakdown.

User Safety Recommendations

Users should:

- Wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet.
- Remove clothing immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing.

3.2 Environmental Hazards

Do not apply directly to water, to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water when cleaning equipment or disposing of equipment washwaters.

3.3 Physical or Chemical Hazards

Spray solutions of this product should be mixed, stored and applied using only stainless steel, aluminum, fiberglass, plastic or plastic-lined steel containers.

DO NOT MIX, STORE OR APPLY THIS PRODUCT OR SPRAY SOLUTIONS OF THIS PRODUCT IN GALVANIZED STEEL OR UNLINED STEEL (EXCEPT STAINLESS STEEL) CONTAINERS OR SPRAY TANKS. This product or spray solutions of this product react with such containers and tanks to produce hydrogen gas which may form a highly combustible gas mixture. This gas mixture could flash or explode, causing serious personal injury, if ignited by open flame, spark, welder's torch, lighted cigarette or other ignition source.

Thomas Sawy

Figure 2: Supplied label of Roundup® product used by Mr. Cervantes

Personal Protective Equipment (PPE)

Mr. Cervantes testified that he wore only long pants and leather work boots as protection when conducting his Roundup® spray application activities. He wore no other protective gear (face shield, respirator, goggles, impermeable Tyvek clothing, waterproof boots, etc.). He occasionally wore absorbent cotton gloves when it was cold.[32]

Mr. Cervantes was asked whether, after reading the product label(s), he felt the necessity to post warnings to the effect that Roundup® had been sprayed. Mr. Cervantes testified that he did not do so as (1) there was no label wording to that effect and (2) he "always talked to the person that I signed the contract with and said, you know, it's not going to go in the lawn, in the grass, and we didn't use it like on a rainy day where it's not going to be effective to blow off and we didn't use it on very windy days just for safety reasons."[33]

Summary of Telephone Interview with Mr. Gerard Cervantes on January 7, 2021

I interviewed Mr. Cervantes by telephone and questioned him on specific aspects of his medical history, exposure to other chemicals and Roundup use.

Mr. Cervantes grew up in Aurora, Illinois; he lived in the same house at [redacted] from age 5 until he joined the Marine Corps in 1977 at age 18. He reported that there were no toxic sites near the residential area and the house which backed up to a corn field. The home was on city water.

Mr. Cervantes' mother developed Hodgkin's lymphoma but had never used Roundup. His biological brother was diagnosed with colon cancer. He has three children (a daughter age 36, a son age 29 and a son age 20); none have cancer.

During high school, he worked as a carpet cleaner and also as a dishwasher at a nursing home.

After his Marine Corps training, Mr. Cervantes was stationed in Adak, Alaska, where he was assigned guard duty of the barracks. He reported that he had no exposure to any toxins while he was there.

Mr. Cervantes reported that he weighed 131 pounds at 5'11" while in the Marine Corps. He weighed between 170 and 190 pounds in his thirties and got up to 215/220 pounds in his early forties. He weighed 215 pounds at the time of his NHL diagnosis.

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[32] Deposition of Gerard F. Cervantes, June 23, 2020, pp. 130, 141.

[33] Id., p. 109.

Mr. Cervantes described the pipe welding he did as an employee of Northern Illinois Gas Company from 1983 to 1987. The pipes were steel natural gas lines that he welded with an oxygen-acetylene blowpipe. There was never freon or any other chemicals in the pipes that he welded. He reported that often in residential installations, before a new fitting could be welded to an existing pipe, the "tar" coating on the pipe had to be knocked off. A cold primer was painted on the pipe before the new fitting was welded. A cold-tar/hot-wrap was then heated with a propane torch and wrapped around the newly-welded pipe to prevent corrosion and rust.

Mr. Cervantes' residential use of Roundup occurred at three properties. He began using Roundup in 1982 at his property at [redacted] where he lived with his wife and his in-laws. Then in 1991, he purchased another property at [redacted] and began using Roundup there while continuing his use at the previous property. The two Spruce Street properties were about the same size, but the [redacted] property had more flower beds.

He continued to maintain both Spruce Street properties until 1996 when he moved to [redacted] This property is much larger and includes a backyard berm which is 15'-18' wide and 80' across. The area is mulched and contains trees and flowers and he sprayed Roundup to kill the weeds. He confirmed that he sprayed once or twice per month from April to November for 1.0 – 1.5 hours per event. His residential spraying was mostly spot-spraying.

Occupationally, Mr. Cervantes provided landscape maintenance which included the use of Roundup. He began spraying Roundup occupationally in 1998, but for the first two seasons, he had only residential customers. During this time period, he sprayed Roundup about **three times per week** for about one hour each time. He reported that he sprayed **each of his properties weekly** throughout the **28-29 week season** from April to November. Beginning in 2000, his business expanded to include several commercial clients such as churches, nursing homes and subdivisions. He estimated that from 2000 through the 2004 season, he sprayed Roundup **three to five days per week each season for 1.5 to 2 hours per day**. The spraying he did for his commercial clients was often widespread carpet-spraying.

Mr. Cervantes primarily used a backpack when spraying Roundup; he switched to the backpack after one year of occupational use. He mixed the Roundup concentrate with water in the backpack on site. When he came in contact with Roundup on his hands, he would usually just wipe them off as he didn't have access to soap and water. He recalled that the residual in the hand sprayer leaked and the trigger leaked Roundup onto his

fingers and both of his hands. The nozzle also leaked, and he recalled that he used to put Teflon tape on it to reduce the leakage.

He used the red cap that came with the Roundup jug to measure the concentrate for mixing in the backpack. He returned the cap back on the container without ever rinsing it.

Mr. Cervantes did not use PPE while spraying Roundup. He usually wore long blue jeans, but sometimes shorts. He always wore work boots and usually short or cut-off sleeves. He wore cotton gloves only in the colder, wet weather in early spring and in the fall.

Mr. Cervantes reported that he would typically bathe with soap at the end of the work day between 9 and 10:00 pm. This was true for both residential and occupational exposures.

Potential Confounding Exposures

Table 1 summarizes toxicological findings pertaining to potential confounding exposures as revealed in deposition and in direct interview on January 7, 2021.

Table 1

Review of Potential Causative Factors

Potential Causative Factor	Yes/No
Family medical history[34]	Yes
Significant alcohol consumption history	No
Smoking history and pack-year calculations	No
Drugs-of-abuse	No
Any history of obesity?	No
Prior significant pharmacological regimens	No
Any history of hematopoietic malignancies or other cancers?	No
Ever been prescribed long-term immunosuppressive pharmaceuticals such as prednisone?	No
Ever prescribed cyclophosphamide or any other drugs to treat cancer prior to NHL treatment?	No
History of organ transplant?	No
Ever been diagnosed with HIV, AIDS?	No
Ever been diagnosed with Hepatitis B or C?	No
Ever been diagnosed with Crohn's disease?	No
Ever been diagnosed with rheumatoid arthritis?	No
Ever been diagnosed with ulcerative colitis?	No
Significant radiological exposures or CT scans prior to NHL treatment?	No

[34] Medical genetics deferred to oncologist.

Table 1

Review of Potential Causative Factors

Potential Causative Factor	Yes/No
Ever lived near or adjacent to a Superfund site?	No
Paint and/or paint solvent exposure?	No
Significant exposures to benzene?	No
Exposure to petroleum products?	No
Any unusual or chronic gasoline exposures?	No
Use of solder for pipe welding?	No
Ever welded pipes?	Yes; oxygen-acetylene
Ever used plumbing PVC glue?	No
Use of a wasp killer or other insecticide/pesticide?	Occasional use of wasp & hornet spray
Use of herbicide other than Roundup?	No
Use of Miracle-Gro?	No
Use of AMDRO?	No
Ever used 2,4-D?	No
Ever used Weed & Feed?	No
Ever used Snake-A-Way?	No
Ever used Sevin?	No
Use of any other home gardening/landscape chemicals?	No
Use of latex paint?	Occasional
Ever farmed or been exposed to livestock?	No
Other underlying chemical exposures?	No

A question of potential asbestos exposure was raised in deposition. The defendant's attorney questioning Mr. Cervantes noted that his physician's medical record contained a statement to the effect that Mr. Cervantes had sustained *"Hazardous exposures - benzene/PCB/asbestos by 30 years."*

Mr. Cervantes stated that he factually related his employment history to physicians and that the statement in the record was how the physician(s) had documented his recitation. His assessment was that the medical record notation was misleading and erroneous.

Mr. Cervantes additionally testified that Nicor management had informed street department personnel that some of the old gas pipes were potentially coated with a substance that may have contained small traces of asbestos. Upon questioning, Mr. Cervantes stated that such exposures were minimal and infrequent. Only some of the older pipes were so coated, and such exposures were uncommon without exposure to loose material.[35]

Similarly, Mr. Cervantes was questioned regarding alleged exposures to benzene. Mr. Cervantes testified that his exposure to the cold tar was minimal. Upon questioning, Mr. Cervantes explained that the assumption of benzene arose from the use of a “cold tar” coating. However, review of all available cold tar products fails to identify benzene in such products.[36]

However, even if such a product contained benzene, it is inconceivable how Mr. Cervantes could receive a significant benzene exposure in the range of 20 to 40 ppm-years in an outdoor environment with exposures of "Three times a week as when I was a welder, but once I was promoted out of that position and I was a lead person, I didn't have to deal with it much because I had a welder on the team and that was -- on the crew and that was his job.”[37] To achieve a dose of benzene significantly associated with the induction of acute myeloid leukemia (AML), a worker would require 40-hours per week of sustained exposures to benzene at the OSHA limit of 1 ppm for 40 years.[38]

Mr. Cervantes further testified that no personal protective equipment was used because "the company informed us that OSHA guidelines stated that it was not required because of the short period of time that it was used as well as outside where we work, the ventilation was adequate and we didn't need any of that."[39]

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[35] Deposition of Gerard F. Cervantes, June 23, 2020, pp. 39-47.

[36] For example, PERMA-PATCH Black Cold Patch, 50 lb. pail produced by Grainger (a common commercial products supplier) does not contain benzene. Ingredients are limestone (95%), asphalt (3.75%) and proprietary ingredients (1.25%). Asphalt does not contain benzene.

[37] Deposition of Gerard F. Cervantes, June 23, 2020, p. 47.

[38] See the report section “Benzene as Potential NHL Risk Factor.”

[39] Deposition of Gerard F. Cervantes, June 23, 2020, pp. 47-48.

Additionally, Mr. Cervantes was questioned regarding alleged exposure to PCBs while employed at Nicor. Mr. Cervantes testified that he had no direct knowledge of PCB exposures and was not aware that such exposures had been mentioned in his personal medical record. He had no knowledge as to whether PCBs were in any way mentioned in the 2006 class action lawsuit. He further noted that he used no other chemicals, pesticides, insecticides or similar substances in the course of his job duties with Nicor.[40]

Scope of Exposures

This section compiles Mr. Cervantes' residential and occupational Roundup® exposures. Compilation is based upon his deposition testimony, plaintiff fact and information sheets and information acquired during his telephone interview on January 7, 2021.[41] Mr. Cervantes noted repeatedly in deposition that he was consistent and meticulous in his residential Roundup® applications at his properties.

Residential Exposure Summary

1. [redacted]

From 1982 to 1996: (14 seasons of mixing and spraying)

- 1-2 events per month from April to November for a total of 7-14 events per season for approximately 1 hour per event.

2. [redacted]

From 1991 to 1996: (5 seasons of spraying)

- 1-2 events per month from April to November for a total of 7-14 events per season for approximately 0.5 hour per event.

3. [redacted]

From 1996 to 2004: (9 seasons of spraying)

- 1-2 events per month from April to November for a total of 7-14 events per season for approximately 1-1/2 hours per event. (Mr. Cervantes testified that the Merrill New Road residence was a much larger property.)

[40] Deposition of Gerard F. Cervantes, June 23, 2020, pp. 49-50.

[41] Interview of Dr. Sawyer with Mr. Cervantes, January 7, 2021.

Occupational Exposure Summary

Prior to 2000, Roundup® applications occurred about three times per week for about one hour each time. Mr. Cervantes reported that he sprayed each of his properties weekly throughout the 28-29 week season from April to November.

Beginning in 2000, his business expanded to include several commercial clients such as churches, nursing homes and subdivisions. He estimated that from 2000 through the 2004 season, he sprayed Roundup three to five days per week each season for 1.5 to 2 hours per day.

Residential Clients

From 1998 to 2000: (2 seasons of mixing and spraying)

- 3 events per week for 28 weeks (from April to November) for a total of 84 events per season for approximately 1 hour per event.

Commercial and Residential Clients

From 2000 through 2004: (5 seasons of mixing and spraying)

- 3 – 5 events per week for 28 weeks (from April to November) for a total of 84 – 140 events per season for approximately 1.5 to 2 hours per event.

Summary of Exposure Factors

Table 2 provides calculations for minimum and maximum exposure days. The table summarizes the prior exposure assessment wherein Mr. Cervantes' exposure factors were reviewed based upon documents, interview and deposition testimony.

Table 2

Cumulative Roundup Exposures and Durations for Gerard Cervantes

Property or Type	Dates & Number of Seasons	Time Period	Events Per Season	Hours per Event	Total Hours	Minimum Exposure Days (8 hrs./day)	Maximum Exposure Days (8 hrs./day)
[redacted]	1982-1996 14	April to November	7-14	1	98 - 196	12	24
[redacted]	1991-1996 5	April to November	7-14	0.5	18 – 35	2	4
[redacted]	1996-2004 9	April to November	7-14	1.5	95 - 189	12	24
Occupational	1998-2000 2	April to November (28 weeks)	84	1	168	21	21
Occupational	2000-2004 5	April to November (28 weeks)	84-140	1.5-2.0	630-1,400	79	175
					Total Minimum & Maximum Exposure Days:	**126**	**248**

Mr. Cervantes sustained a minimum of **126** eight-hour, time-weighted exposure days to a maximum of **248** exposure days with a midpoint value/mean of **187** exposure-days. The descriptions of the Roundup® products used and to which he was exposed, his frequency of spray applications, regularity of exposures and exposure circumstances were obtained from Mr. Cervantes' deposition testimony and verified by telephone interview.

NHL Latency Interval

Based on his first reported exposure to Roundup®, Mr. Cervantes' latency interval to date of diagnosis was approximately **22 years** (1982-2004).

Glyphosate Human NHL Studies

My toxicological opinions with respect to dose are based, in part, on six (6) primary epidemiological studies that provide objective data with respect to several prongs of the Bradford Hill criteria. My toxicological opinion is grounded in animal experimental evidence, *in vitro* human studies and human epidemiological studies as summarized within this report and previously provided by Dr. Portier, et al., in the Federal Daubert motion proceedings. Specifically, I have assessed dose response, temporality, latency period, biological plausibility (toxicological mechanisms), coherence (demonstrated by molecular-based studies) and animal studies as well as the strength of association and consistency with the toxicological mechanisms of Roundup formulation ingredients. I have used the six primary epidemiological studies which include Eriksson, et al., 2008,[42] McDuffie, et al., 2001,[43] Andreotti, et al., 2018,[44] Leon, et al., 2019,[45] Zhang, et al., 2019[46] and Pahwa, et al., 2019,[47] primarily with respect to dose assessment.

My toxicological focus on these studies is on study design, statistical power, and exposure thresholds at different odds ratios, etc. I am using these study results in my toxicological assessment in conjunction with generally-accepted, peer-reviewed studies on genotoxicity (including direct human studies) mechanisms of action (promotion, etc.) absorption, distribution, metabolism, and excretion (ADME), etc. In general, I have relied on studies that have documented the various aspects of the Bradford Hill criteria at or in excess of the 95% confidence threshold. However, I am deferring to the epidemiologist with respect to the internal statistical designs and meta-analysis bio-statistical methodologies employed within each study. Summaries of these six studies are provided below:

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[42] Eriksson, M., et al., "Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis," 2008, International Journal Cancer, Vol.123, pp. 1657 – 1663.

[43] McDuffie H., et al., "Non-Hodgkin's lymphoma and specific pesticide exposures in men: Cross-Canada study of pesticides and health," 2001, Cancer Epidemiology, Biomarkers & Prevention, Vol.10, pp. 1155 – 1163.

[44] Andreotti, G., et al., "Glyphosate Use and Cancer Incidence in the Agricultural Health Study," 2018, JNCI J Natl Cancer Inst., Vol.110 (5), doi: 10.1093/jnci/djx233.

[45] Leon, Maria, et al., "Pesticide use and risk of non-Hodgkin lymphoid malignancies in agricultural cohorts from France, Norway and the USA," 2019, International Journal of Epidemiology, pp. 1–17.

[46] Zhang, L., et al., "Exposure to Glyphosate Based Herbicides and Risk for Non-Hodgkin Lymphoma: A Meta-Analysis and Supporting Evidence," July-September 2019, Mutation Research/Reviews in Mutation Research, Volume 781, pp. 186-206. https://doi.org/10.1016/j.mrrev.2019.02.001

[47] Pahwa, M. et al., "Glyphosate use and associations with non-Hodgkin lymphoma major histological sub-types: findings from the North American Pooled Project," 2019 Jun 27, Scand J Work Environ Health. pii: 3830. doi:10.5271/sjweh.3830

1. **Eriksson, M., et al., 2008 study:**[48] This is a peer-reviewed, case-control study of exposure to pesticides as a risk factor for non-Hodgkin's lymphoma (NHL) in cases in Sweden between 1999 and 2002. Different exposure levels were classified according to days of exposure.

   In this study, the association of glyphosate exposure with non-Hodgkin's lymphoma followed a dose response pattern with an odds ratio (OR) of 1.69 for 10 days of exposure or less, and 2.36 for greater than 10 days of exposure.

   The human epidemiological studies have demonstrated statistically significant increased rates of NHL associated with glyphosate exposure. These studies include several different "exposure day" thresholds: "ever/never," greater than one day and <10 days and greater than 10 days.

2. **McDuffie, H., et al., 2001:**[49] This is a Canadian case-control study which investigated the association of specific pesticides and non-Hodgkin's lymphoma that created dose-response levels based on days/year of personally mixing or applying herbicides. The study revealed that glyphosate exposures between >0 and ≤ 2 days per year had an NHL odds ratio (OR) of 1.0 while exposures greater than 2 days of exposure per year had an NHL odds ratio of 2.12.

   The published McDuffie, et al., study presented "Table 6" in which glyphosate exposure was stratified according to "unexposed," ">0 and ≤2 days," and ">2 days" of per year exposure. The study documented statistically significant dose-responses: an odds ratio of **2.12** (1.20–3.73) for the ">2 days" per year group which was statistically significant.

3. **Andreotti, G., et al., 2018:**[50] The "Agricultural Health Study" (AHS) is an ongoing cohort study which includes 54,251 licensed pesticide applicators from Iowa and North Carolina with 82.8% reporting use of glyphosate. The study is funded by the National Cancer Institute and the National Institute of Environmental Health.[51] An updated

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[48] Eriksson, M., et al., "Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis," 2008, International Journal Cancer, Vol.123, pp. 1657 – 1663.

[49] McDuffie H., et al., "Non-Hodgkin's lymphoma and specific pesticide exposures in men: Cross-Canada study of pesticides and health," 2001, Cancer Epidemiology, Biomarkers & Prevention, Vol.10, pp. 1155 – 1163.

[50] Andreotti, G., et al., "Glyphosate Use and Cancer Incidence in the Agricultural Health Study," 2018, JNCI J Natl Cancer Inst., Vol.110 (5), doi: 10.1093/jnci/djx233.

[51] Id.

evaluation of glyphosate and cancer risk was conducted in the AHS[52] and included cancer incidences through 2012 in North Carolina and 2013 in Iowa. The reported lifetime days' frequency of pesticide application is shown in **Table 3**.

Table 3

Demographics of "Agricultural Health Study"[53] Cohort (Applicators n = 54,251)

Lifetime days of glyphosate use (Quartiles)	Lifetime days of glyphosate use (Tertiles)
1 – 13.74	1 – 19.9
13.75 – 38.74	20 – 61.9
38.75 – 108.4	≥ 62.0
≥ 108.5	

Exposure days can be compared to **Table 3** with the corresponding quartiles or tertiles of the Agricultural Health Study to determine if his exposure was consistent with that of these applicators. The Agricultural Health Study did not find a statistically elevated risk of NHL; however, the study is useful with respect to comparison of other epidemiological studies.

4. **Leon, et al., 2019:**[54] In this analysis combining data from >300,000 farmers or agricultural workers from France, Norway and the USA and accruing more than 3.5 million person-years under risk, the possible association between pesticide use and the risk of lymphoid malignancies was investigated. Specifically, the authors investigated the relationship of the "ever use" of 14 selected pesticide chemical groups and 33 individual active chemical ingredients with non-Hodgkin's lymphoid malignancies (NHL). Pesticide use was derived from self-reported history of crops cultivated combined with crop-exposure matrices (France and Norway) or self-reported lifetime use of active ingredients (USA). Cox regression models were used to estimate cohort specific hazard ratios (HRs) and 95% confidence intervals (CIs) which were combined using random effects meta-analysis to calculate meta-hrs.

   During follow-up, 2,430 NHL cases were diagnosed in 316,270 farmers accruing 3,574,815 person-years under risk. Moderately elevated meta-HRs were seen for NHL overall or certain subtypes with use of specific pesticides compared with "never" use

[52] Id.

[53] Id.

[54] Leon, Maria, et al., "Pesticide use and risk of non-Hodgkin lymphoid malignancies in agricultural cohorts from France, Norway and the USA," 2019, International Journal of Epidemiology, pp. 1–17.

of the same pesticides. In particular, elevated hazard ratios of diffuse large B-cell lymphoma (DLBCL) were seen with glyphosate use (1.36, CI: 1.00–1.85). It is noteworthy that although this study found no association between risk of *all types of NHL overall* and ever use of glyphosate, there was a statistically-elevated risk of borderline significance for DLBCL (the most common type of NHL).

5. **Zhang, L., et al., (2019)**:[55] The Zhang, et al., study is a meta-analysis design that included the most recent update of the Agricultural Health Study (AHS) cohort published in 2018 along with five case-control studies. The study reported that glyphosate-based herbicide (GBH) exposure is associated with increased risk of NHL in humans. Using the highest exposure groups when available in each study, they further reported that the overall meta-relative risk (meta-RR) of NHL in glyphosate-based herbicide exposed individuals was increased by 41% (meta-RR = 1.41, 95% CI, confidence interval: 1.13‑1.75). For comparison, a secondary meta-analysis using high-exposure groups with the earlier AHS (2005) determined a meta-RR for NHL of 1.45 (95% CI: 1.11‑1.91) which was higher than the meta-RRs reported previously.

6. **Pahwa, M. et al., (2019):**[56] In a 2019 study, the associations between glyphosate use and NHL incidence, overall, and by histological sub-type, were evaluated in a pooled analysis of case-control studies. NHL cases were recruited from cancer registries and hospitals in four states between 1991 and 1994, as well as six Canadian provinces. This analysis included 5,131 controls and 1,690 cases of NHL; 647 diffuse large B-cell lymphoma, 468 follicular lymphoma, 171 small lymphocytic lymphoma and 404 other sub-types. The authors found that subjects who had ever used glyphosate had an excess of NHL overall (OR 1.43, 95% CI 1.11-1.83). After adjustment for other pesticides, the OR for NHL overall with "ever use" was 1.13 (95% CI 0.84-1.51) with a statistically-significant association for handling glyphosate more than two days per year (OR 1.73, 95% CI 1.02-2.94, P-trend=0.2). In pesticide-adjusted NHL sub-type analyses, the ordinal measure of lifetime-days was statistically significant (P=0.03) for small lymphocytic lymphoma (SLL) and associations were elevated, but not statistically significant, for “ever years” or “days/year” of use. The authors also showed

[55] Zhang, L., et al., "Exposure to Glyphosate Based Herbicides and Risk for Non-Hodgkin Lymphoma: A Meta-Analysis and Supporting Evidence," July-September 2019, Mutation Research/Reviews in Mutation Research, Volume 781, pp. 186-206. https://doi.org/10.1016/j.mrrev.2019.02.001.

[56] Pahwa, M. et al., “Glyphosate use and associations with non-Hodgkin lymphoma major histological sub-types: findings from the North American Pooled Project,” 2019 Jun 27, Scand J Work Environ Health. pii: 3830. doi:10.5271/sjweh.3830

that subjects handling glyphosate more than two days per year had an excess of DLBCL (OR 2.14, 95% CI 1.07-4.28).

These findings (as summarized in **Table 4**) are consistent with results reported from prior meta-analyses but show higher risk for NHL due to the focus on the highest exposure groups. The authors caution on the interpretation of the numerical risk estimates because of the heterogeneity between the studies.

Nevertheless, all of the evidence from these studies of glyphosate-exposed mice support this association in humans and mechanistic studies of glyphosate-induced immunosuppression/inflammation, endocrine disruption, genetic alterations, and oxidative stress suggest clinically-plausible links between GBH exposure and NHL development. The authors conclude "*The overall evidence from human, animal and mechanistic studies presented here supports a compelling link between exposures to GBHs*[57] *and increased risk for NHL*."

[57] Glyphosate-based herbicides.

Summary of Epidemiological Studies

Table 4 shows the various exposure parameters and assessment metrics for the six (6) epidemiological studies noted herein.

Table 4

Exposure Parameters for Six Referenced Epidemiological Studies[58]

Study	Type of study	Exposure Parameters	
		Metrics (dose intervals)	**Cut-off between Cases and Controls**
McDuffie, H. et al., 2001	Case-control study of men in six Canadian provinces.	Unexposed >0 days and ≤2 days >2 days/year	Cases were diagnosed with STS, HD, NHL or MM between 9/1/1991 and 12/31/1994. Controls did not have NHL diagnoses.
Eriksson, M., et al., 2008	Case-control study of men and women in Sweden	≥1 day and ≤ 10 days >10 days	Cases were newly diagnosed NHL patients aged 18-74 years. Controls were randomly selected from the population registry.
Andreotti, G., et al., 2018	Prospective cohort study of pesticide applicators	Never use Quartiles ranging from 1 day to ≥ 108.5 days Tertiles ranging from 1 day to ≥ 62.0 days	Cases reported ever use of glyphosate. Reference subjects may have used any other pesticides.
Leon, et al, 2019	Pooled analysis of three agricultural worker cohorts	Ever use	Cases reported ever use of glyphosate. Reference subjects may have used any other pesticides.
Zhang, et al., 2019	Meta-analysis	Ever use	6 studies included in primary analysis: one cohort and five case-control.
Pahwa, M. et al., 2019	Case-control study	2 days/year	Subjects handling glyphosate more than two days/year had an excess of DLBCL (OR 2.14, 95% CI 1.07-4.28.

[58] All studies in the table revealed statistically significant increased rates of some type of NHL except Andreotti, et al., 2018. Leon, et al., reported a borderline statistic of 1.36, CI: 1.00–1.85.

Comparisons of Exposure Days to Human Epidemiological Studies

The results of the "exposure-day" calculations (based on validated, reported exposure intervals in the above tables) indicate that Mr. Cervantes' cumulative exposures were above all of the exposure threshold metric cut-offs. That is, he exceeded the *"ever use"* threshold, the *">0 and ≤ 2 days"* threshold, the *">2 days per year"* threshold, the *"≥1 day and ≤ 10 days"* total threshold, and the *">10 days"* total exposure threshold.

Putting this into a dose-metric context, Mr. Cervantes' midpoint of ***187 exposure-days*** exceeds the greatest exposure within the highest quartile of exposure defined as " ≥108.5 days" as defined in the Agricultural Health Study. In fact, his minimum calculated exposure exceeds this value. (Note that no statistically-significant finding of NHL was reported in the Agricultural Health Study). Thus, Mr. Cervantes exceeded the maximum exposure metrics of the cited human epidemiological studies documenting the fact that he was within range of human studies revealing *statistically significant increased NHL cases among glyphosate applicators*.

Unreliable Meta-Analysis of Glyphosate and NHL Risk**

Donato, et al., (2020)[59,60] conducted a meta-analysis systematic review of epidemiological studies on the association between occupational exposure to glyphosate and risk of NHL and multiple myeloma (MM). The results of their study showed no evidence of increased risk of NHL and MM in subjects occupationally exposed to glyphosate. A secondary analysis detected a small increase in risk for the category with the highest level of exposure as well as for DLBCL.

The Donato, et al., meta-analysis has been shown to be not only flawed/unreliable, but of novel design, the findings of which were *unable to be replicated.*[61] Their methodology appears to discredit all previous studies that demonstrate a statistically-significant association between glyphosate and NHL. Rana, et al.,[62] re-calculated the Donato, et al., meta-risk ratios using the same data they used. Donato, et al., reported a meta-relative risk (RR) of 1.03 for never-ever exposure to glyphosate and NHL risk. When replicated, the Rana, et al., study design produced a meta-RR of 1.14 (95% CI = 0.94-1.39).

Another source of discrepancy found was the weighting of original studies selected. Donato, et al., reported the most highly-weighted study (Leon, et al.) was at 74.11%, but according to Rana, et al., calculations, it was only 48.03%. The Leon, et al., study was removed and Donato, et al., reported a mean RR of 1.27, but when Rana, et al., removed this study, they found meta-RR was both increased and statistically-significant (meta-RR 1.34). This shows that further sensitivity analyses should have been conducted to determine sources of heterogeneity.

Overall (and most significantly), none of the Donato meta-analysis results were able to be replicated. Additionally, Rana's group previously conducted a meta-analysis (Zhang, et al., 2019) which was inexplicably absent among the Donato, et al., meta-analysis.

The Donato, et al., findings substantially deviated from Zhang, et al. The discrepancies are reflected in **Figure 3** (*"Table 1"* from Rana, et al). This table is highly significant in that

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[59] Donato, F., et al., "Exposure to glyphosate and risk of non-Hodgkin lymphoma and multiple myeloma: an updated meta-analysis," 2020, Medicina del Lavoro, Vol. 111(1), pp. 63-73.

[60] One of the co-authors, Paolo Boffetta, served as a consultant for glyphosate producers on matters not related to glyphosate.

[61] Rana, I., Taioli, E., and Zhang, L., "Weeding out inaccurate information on glyphosate-based herbicides and risk for non-Hodgkin lymphoma," 2020, Environmental Research, Vol. 191.

[62] Id.

it shows not only the study discrepancies previously noted but also reveals strong consistency in statistical findings between analysis groups.

Table 1. Replicated major findings from the Donato 2020 meta-analysis of glyphosate exposure and non-Hodgkin lymphoma (NHL) model and comparison with Zhang 2019 using random-effects model.

Meta-Analysis	Donato 2020				Replicated Meta-Analysis			Zhang 2019			
Exposure category	N	meta-RR	CI_L	CI_U	meta-RR	CI_L	CI_U	N	meta-RR	CI_L	CI_U
Ever exposure (main analysis)	7	1.03	0.86	1.21	1.14	0.94	1.39	6	1.3	1.03	1.64
Highest (if available)[a]	-	-	-	-	-	-	-	6	1.56	1.12	2.16
Highest only[b]	3	1.49	0.37	2.61	1.49	0.67	3.34	3	1.63	0.97	2.76
Remove Leon 2019 (all case-control studies)[c]	6	1.27[d]	0.92	1.61	1.34[d]	1.04	1.73	5[d,e]	1.84	1.33	2.48
Cell-type specific											
DLBCL (ever)	3	1.31[d]	0.93	1.7	1.32[d]	0.99	1.76	-	-	-	-
MM (ever)	3	1.04	0.67	1.41	1.15	0.76	1.74	-	-	-	-

ABBREVIATIONS
CLL, chronic lymphocytic leukemia; CI, confidence interval; DLBCL, diffuse large b-cell lymphoma; N, number of studies; meta-RR, meta-analysis relative risk.

NOTES

a Zhang 2019 used high exposure category when reported and ever-exposure for all other studies.

b Only three studies that reported high exposure categories were used. For Andreotti 2018, Zhang 2019 selected highest intensity weighted lifetime days lagged by 20 years or more whereas Donato 2020 selected highest days per lifetime.

c The remaining studies are all case-control. In their analysis of all case-control studies, Zhang 2019 follows the *a priori* selection criteria and has (N=6) because Cocco, 2013, was not included in the analysis.

d Fixed-effects model was used because between-study heterogeneity, defined as the X^2-test statistic for heterogeneity being greater than its degrees of freedom (number of studies minus one), was not detected. Use of fixed-effects model was not reported in Donato 2020.

e Leon 2019 was not used in Zhang 2019 although it included data from Andreotti 2018. Thus, Andreotti 2018 was removed to conduct an analysis of only case-control studies.

Figure 3: Data discrepancies between Donato, et al., meta-analysis, replicated meta-analysis and Zhang, et al., meta-analysis[63]

Study differences between Donato, et al., and Zhang, et al., included study selection, statistical analysis model and exposure category selection. Zhang, et al., used Andreotti, et al., which reported exposure estimates stratified by level whereas Donato, et al., used recently published pooled analysis by Leon, et al., that reported only "never-ever"

[63] Id.

exposures. Donato, et al., used a hierarchical regression model whereas Zhang, et al., used logistical regression.

Overall, fundamental errors or differences in methodological reasoning (study selection, statistical modeling and imprecise definitions of categories) contributed to the flawed conclusions reported in Donato, et al. When Zhang, et al., conducted a sensitivity analysis using a hierarchical regression model in their study, they found the meta-RR to be **1.46**. Zhang, et al., reported both fixed-effects and random-effects models whereas Donato, et al., indicated that they reported only random-effects model. Zhang, et al., followed *a priori* criteria to select the highest exposure category when it was available whereas Donato, et al., used never-ever exposures. When dose-response analyses were attempted, Donato, et al., failed to describe exact criteria of how their highest exposure category was selected.

It appears that exposure frequency was prioritized but it remains unclear why this metric was selected as it does not factor in exposure intensity. Conversely, Zhang, et al., clearly listed the order of selection of the most highly-exposed category based on the *a priori* hypothesis and current scientific understanding of NHL risk.

If the *a priori* hypothesis were followed, the meta-RR from the same three studies used in Donato, et al., would increase to **1.63**. Rana, et al., also compared risks for never-ever exposures to the highest exposure groups and found the meta-RR increased by 35% in their replicated analysis of Donato, et al., and 33% in Zhang, et al., indicating the presence of an exposure-response relationship in both analyses.

Furthermore, the Rana, et al., study clearly defines a “high” exposure group at a level relatively greater than other exposed categories. The “greater than two days of exposure per year” (>2d/y) group contains individuals exposed to glyphosate-based herbicide (GBH) at routinely used agricultural spray concentrations and not at high levels. In fact, Rana, et al., believe that the 41% increased RR of NHL reported in Zhang, et al., still underestimates the true risk. Thus, due to timing of GBH exposures and study subjections recruited in original individual studies as well as the potential latency of NHL, the meta-RR in Zhang, et al., may have been underestimated.

Most studies included in their meta-analysis were conducted prior to the exponential increase in glyphosate use and evaluated cancers that developed prior to 2013. The Eriksson, et al., study captured exposures well before the exponential increase in glyphosate use. Despite this fact, the study still detected a positive dose-response

relationship. Even in the most recent Leon, et al., study, the follow-up periods of each of the cohorts was still limited to about 10 years ago indicating that the current, true NHL risk has yet to be uncovered especially with the significant increase in exposures in recent years.

Another emerging finding that the DLBCL subtype may be more strongly associated with GBH exposure could further underestimate the Zhang, et al. ,meta-RR of NHL. Analyzing NHL as a whole would attenuate potential associations which were reported in Leon, et al.

In summary, Rana, et al., concluded that the findings of their re-analyses **do not support the conclusions drawn by Donato, et al**. Almost none of the calculations were reproducible with the exception of a funnel plot. This demonstrable lack of transparency regarding details and definitions of high-exposure categories raises serious concerns about the reliability of this study.

Personal Protective Equipment (PPE) and Measured Dermal Exposure Levels

It is generally recognized that personal protective equipment (PPE) constitutes an essential part of safe preparation, application and handling of potentially hazardous substances. With the exception of eye exposure warnings, the Roundup label has not provided sufficient toxicological warning information or PPE requirements. The WHO established a protocol for field surveys of exposed applicators to "*organophosphorus pesticides*" as well as a summary of the "*protective measures needed to be implemented to ensure safe use*" in 1981.[64] Liquid aerosol from an herbicide such as Roundup can be absorbed by exposed skin and/or by penetrating through clothing which comes into prolonged contact with skin. Such dermal absorption routes have been previously assessed in toxicological dose assessment studies (including studies by Monsanto).

Quantification of these routes of exposure must be based on objective, factual information to determine the dose contributed by each defined route. For example, early studies as

[64] World Health Organization, "Field Surveys of Exposure to Pesticides", VBC/82 .1.

cited by Machado-Neto, et al., of knapsack sprayers reveal that hands presented only 10 to 25% and legs 25 to 85% of the total dermal exposure route.[65]

Penetration of Glyphosate through Clothing

Studies using gauze patches on the inside and outside of garments (paired patches) such as pants, shirts, etc., have been conducted to determine the penetration of glyphosate through clothing. Such studies use laboratory analyses to measure glyphosate or surrogate markers on each side of the fabric to determine the percent penetration.

A study of highly-protected glyphosate applicators concluded, "*Nevertheless, average values for all paired patches showed an average of 22.9% of the glyphosate deposited on worker clothing might be expected to penetrate through it*."[66]

The applicators in this study wore protective clothing that consisted of a protective suit, rubber gloves and boots. Spraying was performed by placing a metal, cylindrical shield on the end of the wand (a spray chamber) around each weed and then releasing only about 0.5 ml per spray which targeted the weeds without drift; thus, protecting nearby seedlings. Glyphosate deposition was analyzed from paired glyphosate collection patches on the outside and inside of the clothing worn by workers.

A recent study by Spaan et al.,[67] investigated exposure data, including actual dermal exposure (ADE) and potential dermal exposure (PDE), from three field study databases (BROWSE, ECPA, and BfR agricultural operator exposure model databases) which were analyzed to determine migration of pesticides through protective clothing for a more realistic assessment of occupational exposure to pesticides rather than just based on laboratory tests (which may overestimate the protective factor of garments). Migration was calculated by dividing the ADE and PDE then multiplying by 100 to obtain a migration value (percent). Estimation of migration was based on data from individual body parts and combining PDE and ADE values for all body parts in order to assess performance of garments for individual body parts and whole garments. For individual body parts, it was found that large variability in migration occurred, up to 99%, but in general, a limited level

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[65] Van Hemmen, 1992 *in* Machado-Neto, et al., "Safety of Working Conditions of Glyphosate Applicators on Eucalyptus Forests Using Knapsack and Tractor Powered Sprayers," 2000, Bull. Environ. Contam. Toxicol., Vol. 64, pp. 309-315.

[66] Lavy, T. et al., "Conifer Seedling Nursery Worker Exposure to Glyphosate," 1992, Arch. Environ. Contamin. Toxicolo. Vol.22, pp. 6-13.

[67] Spaan, S., et al., "Performance of a Single Layer of Clothing or Gloves to Prevent Dermal Exposure to Pesticides," 2020, Annals of Work Exposure and Health, pp. 1-20.

of 2.3% mean migration was observed with 75% of distribution below 9.3%. A higher percent of migration of pesticides was observed in garments that protected the body as compared to gloves. Mean migration through whole garments was 2.6% with 75% of distribution below 7.2%, with variability up to 71%. The results of this study indicate that laboratory tests may overestimate the protective factors of garments compared to field studies (real conditions). In both individual body parts and whole garment, more migration occurred during mixing/loading operator tasks as compared to mixing/loading and application together and application alone.

Lack of Personal Protective Equipment (PPE)

The presence of systemic glyphosate in humans has been well documented and previously reported.[68] Acquavella, et al., performed biomonitoring of 48 farmers, their spouses and 79 children (4-18 years) for glyphosate in urine the day before as well as one and three days after glyphosate application (tractor and boom). They reported detectable levels of glyphosate in urine on the day of application in sixty percent of the farmers (geometric mean was 3 ppb; the maximum value was 233 ppb and the highest estimated systemic dose was 0.004 mg/kg). The maximum value of 233 µg/L was from a farmer whose teenage son also had the highest urinary concentration of 29 µg/L among children. Farmers who did not use rubber gloves had five times more glyphosate in their urine than those wearing protective gloves.

Various glyphosate-based formulas were used with various surfactants and/or salts. The proportions of participants with detectable urinary glyphosate differed between the two states: 87% detection rate in South Carolina; 36% in Minnesota. The urine concentrations were similarly different: 7.9 µg/L on day of application in South Carolina; 1.4 µg/L on day of application in Minnesota. The proportion of applicators wearing rubber gloves in Minnesota (96%) was much greater than that in South Carolina (43%) suggesting that the use of gloves is responsible for the differences seen. It is interesting to note that a similar proportion of glove-wearing applicators was reported by Alavanja, et al., in 1999: 39% in North Carolina; 76% in Iowa.

A study of farmers' application of pesticides (mostly glyphosate-based formulations) in the Nanumba area documented that a typical farmer's usage of pesticides did not follow safe practices. Of 100 farmers, only 55% indicated that they checked pesticide label

[68] Acquavella JF, Alexander BH, Mandel JS, Gustin C, Baker B, et al., "Glyphosate biomonitoring for farmers and their families: results from the Farm Family Exposure Study," 2004, Environ Health Perspect 112, pp. 321-326.

information while 42% indicated that they used pesticides without checking labels. Modeled farmer exposure to glyphosate was noted to be 0.3 mg/kg/BW/day on average (0.7 mg/kg-BW/day 95th percentile) when full personal protective equipment (PPE) was used and an average of **4.2 (8.1 – 95th percentile) mg/kg-bw/day when PPE was not used**. It is noteworthy that 90% of the farmers reported to have never used masks, face shields, goggles or full respirators; less than 30% of the farmers reported using impermeable clothing. In terms of pesticide sprayed, farmers' dosing ranged widely including 9% of the farmers applying high doses between 7 and 12 L/ha and 3% of the farmers applying doses as high as 13 - 15 L/ha. These extremely high doses of herbicide were reported by those who use it for both land clearing and weeding.[69]

Dosemeci, et al.,[70] developed two algorithms to estimate long-term pesticide exposures by utilizing an enrollment questionnaire and a take-home questionnaire in the Agricultural Health Study Cohort of 58,000 pesticide applicators. Intensity level was determined based on applicators' exposure factors. In both algorithms, PPE was a major factor. In the detailed algorithm, additional factors were included such as washing pesticide equipment, replacing old gloves, personal hygiene and changing clothes. A total quantitative exposure score was determined by a formula based on intensity level, duration of exposure and frequency of exposure. The take-home questionnaire population (sub-cohort of applicators) represented the enrollment population (entire cohort of applicators) in terms of evaluation of health risk as they both showed similar intensity of exposure and distribution of exposure levels by demographic variables. With PPE being a major exposure factor, reduced or no PPE made a significant difference in the intensity level. Intensity was greater for no or little PPE which reflects more residential users versus occupational users in which PPE is typically used.

According to Wumbei, et al., 2019, human exposure to herbicides can occur due to accidents while mixing, loading or applying pesticides or contact with treated crops during field re-entry. The study notes that the risk of harm to the farmer is greater during mixing than during application. A quote by a farmer states "*Some of us do not care about how close they spray to water bodies. Some of us who farm along streams sometimes spray directly into the streams and still drink from these streams, especially the rice farmers. In fact, people are joking with the pesticides over here. Some people in the process of*

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[69] Wumbei, A., et al., "Pesticides use and exposure among yam farmers in the Nanumba traditional area of Ghana," 2019, Environmental Monitoring Assessment, 191:307, DOI: 10.1007/s10661-019-7449-5

[70] Dosemeci, M., et al., "A Quantitative Approach for Estimating Exposure to Pesticides in the Agricultural Health Study," 2002, Ann. Occ. Hyg., Vol. 26 (2), pp. 245-260.

preparing the spray solution will even put their finger into the solution and put it at the tip of their tongue to know if the solution is strong enough to kill the weeds very well."

Dermal Exposure of Glyphosate Applicators

The dermal contact exposure of glyphosate applicators was determined by Machado-Neto, et al., 2000.[71] In these studies, applications were conducted under different scenarios, both with and without personnel protective equipment. Potential dermal exposure was measured by the authors by the use of a copper fungicide added to the Roundup spray solution as a surrogate metric. That is, Cu+2 cations were measured in the laboratory from *"Carefree"* female sanitary pads placed on the exterior of the clothing.

These sanitary pads were externally affixed to eight defined areas of each worker's body. These included a) head, face and neck, b) arms and forearms, c) hands, d) thorax front, e) thorax back, f) legs and front thigh, g) legs and back thigh, and h) feet. Personal dermal exposure (PDE) in hands was directly measured by analysis of the cotton gloves used by workers. Total body exposure via the dermal route (in units of mg/day of glyphosate) was established with percentages determined for each of the eight different body areas with and without PPE.

For "knapsack" (i.e., backpack) sprayers using a lever pump sprayer, total dermal exposure measured 1,945.83 mg/day versus 253.90 mg/day with PPE. In calculation of actual dermal exposures, penetration through fabric of the PPE (overalls and hoods) was referenced at penetration values of 20%, 5% for boots, 1% for rubber gloves and 1% for facial masks. Dermal absorption of 2% was then used by Machado-Neto, et al., to calculate dosage.

Absorptions from 70-minute exposure periods were extrapolated to provide values equal to absorption sustained in a theoretical work day. **Table 5** shows the proportion (%) distribution of personal dermal exposure (PDE) for various body regions for glyphosate applicators using a lever-operated knapsack sprayer as published in the 2000 Machado-Neto study.[72]

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[71] Machado-Neto, et al., "Safety of Working Conditions of Glyphosate Applicators on Eucalyptus Forests Using Knapsack and Tractor Powered Sprayers," 2000, Bull. Environ. Contam. Toxicol. Vol. 64, pp. 309-315.

[72] Id.

Table 5

Distribution of PDEs in Body Regions of Glyphosate Applicators

Type of Sprayer	Glyphosate Concentration	% of Body Regions							
		A	B	C	D	E	F	G	H
Lever-operated Knapsack	0.48%	0.1%	0.5%	4.3%	1.6%	0.1%	44.6%	7.7%	41.1%
		A = head + face + neck B = arms + forearms C = hands D = thorax front				E = thorax back F = legs + front thigh G = legs + back thigh H = feet			

These results are significant in the current matter. The table notes that the highest percentages of exposed body regions are (1) legs+front thigh and (2) feet. These areas are very significant as the plaintiff reported wearing mesh-type tennis shoes and shorts while spraying.

Table 6 shows the published 2000 Machado-Neto study results of glyphosate dermal exposure (in mg/day) expressed as "Potential" exposure and as "NCDE" (Not Controlled Dermal Exposure). This table is also significant in the current matter as it clearly demonstrates the potential difference in exposure between sprayers wearing personal protective equipment and those not wearing such equipment. Sprayers who did not wear PPE received **7.6 times higher** dermal exposure than those who wore PPE.

Table 6

Potential Dermal Absorption (without any PPE) and Not Controlled Dermal Exposure (NCDE) with Personal Protective Equipment

Type of Sprayer	Glyphosate Concentration	Dermal Exposure (mg/day)	
		Total dermal exposure	Exposure with PPE
Lever-operated Knapsack	0.48%	1,945.83	253.90

Example of Roundup Exposure of 1,4-dioxane (no gloves, short sleeves)

Authored by Dr. William Heydens, Monsanto Senior Toxicologist, (Mon# MONGLY00154342 (Volume 1) and MONGLY00154381 (Volume 2)

In 1990, Monsanto submitted two reports (risk assessments) in support of glyphosate registration in Canada and the U.S. These assessments were prepared to address

concerns that arose when 1,4-dioxane (a contaminant in Roundup which is a substance characterized by IARC as "possibly carcinogenic to humans") was detected in Canada's Roundup (Vision Herbicide) in 1989.

Volume 1 of their assessment, *"Cancer Risk Assessment for Agricultural and Forestry Applications of Herbicide Surfactant Containing 1,4-Dioxane,"* was prepared for and submitted to Health and Welfare Canada and Agriculture Canada. Volume 2 of their assessment, *"Cancer Risk Assessment for Agricultural and Roadside Applications of Herbicide Surfactant Containing 1,4-Dioxane,"* was prepared "to address concerns more specific to California"[73] and was submitted to CDFA.[74]

To determine exposure, Monsanto examined 28 studies in the U.S. Environmental Protection Agency's generic data base for base exposure data (*i.e.* pesticide active ingredient, dermal deposition and inhalation exposure rates). Monsanto utilized the reported *median* values for their assessments claiming they are more reliable estimates of exposure than mean values and, therefore, yield more realistic assessments of risk. Monsanto found that the mean exposure value was 2.8 times higher than the median for workers with gloves and long sleeves and 2.2 times higher for workers without gloves and long sleeves. Thus, only the *mean* values were utilized. Monsanto characterized these results as a "*worst-case*" risk assessment for the U.S. (Volume 2).[75]

It is notable that in Monsanto's *"worst-case"* scenario, the maximum concentration of dioxane in the formulation is 23 ppm. In the Canadian assessment, however, Monsanto reports that, after conducting extensive analyses on retained product samples located at various Monsanto manufacturing and research technology locations, the mean 1,4-dioxane concentration was **160** ± 56 ppm with a range of 56 - 307 ppm.

The reason for this seeming disparity is that just prior to their assessments,[76] Monsanto changed their formulation requirements such that no more than 23 ppm 1,4-dioxane would be contained in the herbicide concentrate. The median exposure values Monsanto published in their Volume 1 assessment for tractor boom application in both an open cab and closed cab are presented in **Table 7** below.

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[73] Page 004 of 0029.

[74] California Department of Food and Agriculture.

[75] Monsanto noted this to be a "*worst case approach*" although they used a lower dose (23 ppm vs. 300 ppm) of 1,4-dioxane in this assessment.

[76] The time of the requirement change in Canada and/or US is not reported.

Table 7

Median Values for Combined Dermal and Inhalation Exposure

Protective Clothing Worn	Exposure (Open Loading/Mixing) (µg/pound of active ingredient applied)	Exposure (Closed Loading/Mixing) (µg/pound of active ingredient applied)
Long sleeves, gloves, long pants	19.3	1.9
Short sleeves, no gloves, and long pants	75.6	7.6

As shown in Table 7, the exposure in both cases is approximately **four times greater** for workers wearing short-sleeved shirts without gloves than for workers wearing long sleeves and gloves.

Monsanto's Volume 2 risk assessment results for tractor boom application in an open cab using an open transfer system were based on mean exposure values as given in **Table 8**. The exposure for applicators wearing short sleeves and no gloves is three times greater than the exposure for applicators wearing long sleeves with gloves.

Table 8

Mean Values: Combined Dermal and Inhalation Exposure for "Worst Case Scenario"[77]

Protective Clothing Worn	Exposure (µg/pound of active ingredient applied)	Exposure (µg/kg/year)
Short sleeves, no gloves	165.7	7.79
Long sleeves and gloves	54.47	2.56

Again, these factors illustrate the profound difference in exposure between sprayers who wore protective equipment and those who did not.

Omission of PPE Labeling Recommendations by Monsanto

Monsanto conducted a formal operator exposure assessment (MON 2139) and evaluated exposure when spraying Roundup under UK conditions. A series of spray volume and dose combinations were presented and assessed. As a consequence of the results, a series of specific label recommendations were set forth in the Monsanto report.

Table 9 summarizes the published label recommendations as noted in the Monsanto MON 2139 document and their resulting presence in actual Roundup product label(s):

[77] Tractor boom application with an open cab and open loading/mixing conditions.

Table 9

Summary of MON 2139 Label Recommendations and Resulting Label Inclusions

Condition	Recommended PPE by Monsanto Scientists	Included in Current Label	Notes
"When handling or applying the concentrate"	Protective gloves	Yes	*"When mixing"*
	Face protection (face shield)	**NO**	
"When spraying through ultra-low volume application and mist blower equipment"	Coveralls	**NO**	
	Protective gloves	Yes	*"When mixing"*
	Rubber boots	**NO**	
	Face protection (face shield and dust mask)	**NO**	
"When using low volume nozzles in knapsack sprayer, handheld rotary CDA sprayers and handheld weed wiper equipment"	Water-proof jacket	**NO**	
	Water-proof trousers	**NO**	
	Protective gloves	Yes	*"When mixing"*
	Rubber boots	**NO**	

The Roundup test applications were conducted outdoors in Florida and the results were only for hand-pumped, backpack-type sprayers. Sampling techniques were designed to establish exposure on the basis of inhalation, aerosol deposited on exposed skin and the amount that may deposit on covered skin.

Deposition on skin was estimated by attaching 11 (eleven) 10x10 cm surgical pads at strategic locations on the applicator's body as follows:

Exposed Surfaces		Under Clothing
Top of head	Back	Right forearm
Forehead	Right bicep	Left bicep
Chest	Left forearm	Ankle
Shoulder	Thigh	

Additionally, separate estimations were made for the amount of glyphosate that may contaminate the operator's hands when wearing cotton gloves. It was presumed this technique would yield maximum exposure levels as the gloves would absorb any spills which could be wiped or washed off the hand. The published results are shown in **Figure 4** below.

- *Potential exposure (Glyphosate found on operator clothing + unprotected skin)*

Measured exposure (µg/cm^2) is given for each body part in table 7.

Table 7: MSL-0288 exposure (µg/cm^2)

Clothing type	Quantity of Glyphosate found (µg/cm^2)		
	Test 1	Test 2	Test 3
Gloves			
Left	0.014	1.98	6.56
Right	0.006	2.00	3.22
Exposed Gauze pads			
Head	--	--	--
Forehead	--	0.033	0.012
Shoulder	0.033	0.116	0.235
Chest	0.017	0.083	0.245
Back *	6.38	5.96	3.99
Thigh	0.96	0.18	1.39
Right bicep	0.090	0.058	0.253
Left forearm	0.051	0.098	0.377

* Highest exposure values were observed on this pad. This was expected as the sprayer is resting on this pad allowing pickup of any spillage.

Figure 4: *"Table 7"* from Monsanto MON 2139 Study Showing Results of Exposure Tests

Key Points Pertaining to Exposed Body Parts

- The ug/cm^2 exposure to glyphosate reveals significant exposure to nearly all body areas (except forehead and head which were not consistently exposed).
- POEM model includes stated exposure percentages for different parts of the body in peer-reviewed literature for applicators and in Monsanto's own in-house studies.
- Monsanto employees were protected with PPE in all exposed body areas stated during their tests, but consumers are not protected because the product label provides no such instructions (in spite of the fact that Monsanto's own report recommended specific warnings).

- In earlier reports submitted in the Monsanto litigation matters, Dr. Sullivan (an expert retained by Monsanto) has only calculated leg and hand exposures. More recently, Monsanto's expert Dr. LeBeau (report dated 9-3-2019) also failed to include other body areas. All other exposed areas were ignored. This represents a gross deviation from accepted assessment methodology.

3. Glyphosate Exposure & Toxicity

Exposure models have been developed in the last 20 years that are used to estimate the exposure dose of professional operators to biocides during application. The accuracy of these models' ability to assess actual exposure is primarily determined by the pharmacokinetic studies and assumptions used in developing the model (such as dermal absorption rate and other variables).

PK models (pharmacokinetic models) simulate the absorption, distribution, metabolism and excretion (ADME) within a living system. Biomonitoring and dosimetry data are combined with PK models to reconstruct or estimate the exposure dose. It is, therefore, essential to have a good understanding of the pharmacokinetics to ensure a good estimate of the exposure dose.

Monsanto's Glyphosate Biomonitoring and Dose Measurement Reliability

Monsanto has officially postured its glyphosate formulations as *"trade secrets"* (and thus remain unpublished). As a consequence, the general scientific community has had minimal opportunity to assess the toxicity of the various glyphosate product formulations, many of which contain surfactants and other substances.

This is perhaps a peculiar position in which to find the world's most ubiquitous herbicide, but it is nevertheless a fact. It is also a substantial limitation for toxicological assessment.

As a consequence of non-disclosures, there are discrepancies and differences of opinion as to the pharmacokinetics (or ADME) of glyphosate which have not been entirely assessed in the peer-reviewed literature.

However, Monsanto has conducted some limited in-house studies and internal Monsanto communications recognize the limitations of these studies. As [redacted], the head of Monsanto's Regulatory Affairs Unit, wrote:

> *"ADME has always been the weak link in our argument…we have not got rid of that problem."*[78]

When assumptions in a critical, Monsanto-contracted pharmacokinetics study were questioned by Spanish regulators, Monsanto corporate employee, [redacted] wrote,

> *"Even though we can absorb additional 'uncertainty factors' in our risk assessment based on our biomonitoring results, I feel uncomfortable with this discussion. This approach by Spain sets a precedent and contradicts the fact that we always claimed to fully understand the glyphosate pharmacokinetics."*[79]

Additional information is contained within an unpublished Monsanto study in which the percentage of dermal absorption was shown to be as high as 10% (TNO rat skin study). Since dermal exposure is the most significant route of exposure, a small change in the percentage of dermal exposure can have a great effect on the overall exposure. Monsanto acknowledges this fact directly in a July 2001 draft:

> *"One of the product specific parameters that can make a big difference in the exposure assessment is the dermal uptake factor which is the fraction of the amount of active ingredient on the skin surface that is absorbed by the skin tissue."*[80]

In an August 16, 2011, email regarding dermal absorption, [redacted] wrote:

> *"In Europe, we are getting prepared to submit MON 79991 (720 g/kg) for approval under the new Reg 1107/2009. We ran the UKPOEM model using a dermal penetration value of 3% and do not pass when applying 3.6 kg/ha for the tractor-mounted sprayer. I am aware of the set of studies that you ran on dermal absorption using pure K-salt and IPA-salt and also MON 52276 and MON 79351 which showed dermal absorption values of 1%. Putting 1% in the model, we get a good result, so will need to show that the 1% dermal absorption numbers are equally valid for the MON 79991 formulation."*[81]

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[78] MONGLY02221147.

[79] MONGLY02155829.

[80] [redacted] July 2001, Confidential draft, "Clustering glyphosate formulations with regard to the testing for dermal uptake."

[81] MONGLY04107779.

Glyphosate (Roundup) History and Use

Glyphosate is the active ingredient in various Roundup herbicide formulations. The Monsanto Company discovered the herbicide activity of glyphosate in 1970 and initiated sales and distribution for weed control in 1974. Glyphosate is not selective and is used on food and non-food crops. Over the subsequent four decades, glyphosate use as an herbicide has greatly expanded. It is used in agriculture, forestry, industrial right-of-ways and in residential applications worldwide.

Glyphosate's use in agriculture has been further expanded by the development of genetically-modified plants that are tolerant to glyphosate treatment (Roundup-Ready®).[82] This has significantly increased the use of glyphosate on these crops for weed control with no concern for crop injury.[83] As a result, genetically-modified crops contain far more glyphosate residue than conventional crops.

The introduction of glyphosate-resistant (GR) crops in 1996 and the expiration of the glyphosate patent have resulted in its ubiquitous use today characterized by a 15-fold global increase since the mid-1990s.[84]

According to glyphosate pesticide registration, in 1993, approximately 13 to 20 million acres of land had been treated with 18.7 million pounds of glyphosate and used mostly on hay/pasture, soybeans and corn.[85] According to the U.S. Geological Survey, in 2014, 300 million pounds of glyphosate were used on agricultural land in the U.S. Since 1974, over 3.5 billion pounds of glyphosate have been applied in the US.[86]

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[82] Williams, G. et al., Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans," 2000, Regulatory Toxicology and Pharmacology, Vol.31, pp. 117-165.

[83] Duke, S. S., "Encyclopedia of Agrochemicals," 2003, John Wiley & Sons.

[84] Benbrook, C.M., "Trends in glyphosate herbicide use in the United States and globally," 2016 Environmental Sciences Europe. 28:3.

[85] U.S. EPA, "Registration eligibility decision-facts: Glyphosate," 1993 United States Environmental Protection Agency, Prevention, Pesticides and Toxic Substances (7508W), EPA-738-F-93-011.

[86] Benbrook, C.M., "Trends in glyphosate herbicide use in the United States and globally," 2016, Environmental Sciences Europe. 28:3.

Contaminants within Roundup (Surfactants, Adjuvants and Co-formulants)

A 2017 toxicological study[87] by Tarazona, et al., reviewed the scientific basis of glyphosate's carcinogenic classification and offered the following guidance with respect to contaminants in glyphosate and Roundup surfactants, adjuvants and co-formulants:

> "Surfactants are frequently used in herbicide formulations including glyphosate. Polyethoxylated tallowamines are several orders of magnitude more cytotoxic than glyphosate (Mesnage, et al., 2013); the mode of action is cell death with inhibition of the mitochondrial succinate dehydrogenase activity and membrane damage leading to necrosis. This mode of action is different from glyphosate while similar to that observed for glyphosate-based formulations (Benachour and Seralini, 2009). These tallowamines also produce oxidative and DNA damage (Nobels, et al., 2011), and increase the apoptotic potential of glyphosate (Kim, et al., 2013). Other surfactants as well as solvents used in pesticides formulations are cytotoxic and possibly genotoxic (Nobels, et al., 2011)."

It will be seen in the following data tables that a variety of substances have been added to the product to increase or enhance absorption. Unfortunately, it has not been possible to assess the actual constituent components of Roundup surfactants because (in the U.S.) such mixtures are protected as "proprietary" formulations. For example, the label on Roundup Original Max herbicide (which contains a proprietary surfactant) merely states "Other Ingredients: 51.3%." In other words, more than half of the volume of the product consists of water and unknown substances.

Without good information, substance toxicity cannot be scientifically or toxicologically evaluated with reliance and accuracy. It should be further noted that individual chemical assessment is the recommended worldwide method for carcinogenic substances as highlighted in the previous document:

> The UN and EU guidance recommends carcinogenicity and genotoxicity studies to be conducted on individual chemicals, limiting testing of mixtures/formulations to cases where synergistic effects are expected (United Nations 2015).[88]

Table 10 lists the various substances in Roundup formulations, depending on years of exposure and type of Roundup product used.

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[87] Tarazona, et al., "Glyphosate toxicity and carcinogenicity: a review of the scientific basis of the European Union assessment and its differences with IARC," National Institutes of Health, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5515989/

[88] Id.

Table 10

List of 22 Chemicals Known to be Present in Roundup Based on Product Labels[89] and Potentially Used by Plaintiff Based on Product and Year

Compound/Substance	Years Label Shows Used in Roundup
1-dodecanamine (surfactant)	1999
Ammonium Sulfate	2002
Antifoam ("A," "AF," "C")	1999
Antimicrobial Agent	1992, 1995, 1998, 2002
Dimethyl polysiloxane	1995
Dipropylene glycol	1998, 2002
Glyphosate	1992, 1995, 1996, 1998, 2002
MON 013962 Technical Solution	1999
Nonanoic acid	1998, 2002
Pelargonic acid	1992, 1995, 2002
Polyoxyethylene alkyl amine	2002
Polyoxyethylene alkyl phosphate ester (surfactant)	1999
Polyoxyethylene alkylamine (surfactant)	1992, 1995, 1999
Potassium hydroxide	1992, 1995, 1998, 2002
Propylene glycol (co-solvent)	1999
SAG 10	1999
SAG 30	1999
Silicone emulsion	1999
Silicone emulsion (dimethylpolysiloxane)	1998, 2002
Surfactant Blend (tallowamine, glycerine)	2002
Surfactant Mon 59112	1996, 1998, 1999, 2002
Water	1992, 1995, 1996, 1998, 2002

There are several critical points to note with respect to this formulation chronology:

- The basic product formulation has not changed significantly over the years.

[89] Product formulation data provided by Monsanto in response to Interrogatory demand for only certain years. These years correspond to years the products were used by Plaintiffs. No product formulation data was provided for U.S. EPA registration years 1993, 1994, 1997, 1999, 2001 or 2003-2008.

- Although every product contains surfactants in various forms, the word “surfactant” only appears in selected years. Labels often substituted different POEAs as a specific surfactant. Sometimes a proprietary mixture is presented in abbreviated form.

Table 11 presents a detailed breakdown of the various Roundup formulations available based on product labels available for assessment.

Table 11

Roundup Formulations potentially used by Plaintiffs - Chemicals within Glyphosate and Roundup Surfactants, Adjuvants and Co-formulants

Product Brand Name	Formulation(s)
Roundup Ready-To-Use Weed & Grass Killer EPA Reg: 71995-08 (7/13/1992)	Glyphosate - 1%; Polyoxyethylene alkylamine 0.36%; Water - 97.129 %; pelargonic acid 1%; Potassium hydroxide 0.45%; Antimicrobial Agent; 0.1%;
ROUNDUP Super Concentrate Weed & Grass Killer 2 (12-3-1999)	MON 013962%Technical Solution (N-phosphonomethylgtycine, IPA salt) CAS# 38641-94-0 Polyoxyethylene alkylamine (surfactant) Polyoxyethylene alkyl phosphate ester (surfactant) Propylene glycol (co-solvent) 1-dodecanamine (surfactant)
Roundup Ready-To-Use Weed & Grass Killer [1] EPA Reg: 71995-12 (8/16/1995)	Glyphosate - 1.55%; Polyoxyethylene alkylamine 0.36%; Water - 95.99 %; pelargonic acid 1%; Potassium hydroxide 1.0%; Antimicrobial Agent; 0.1%; Dimethyl polysiloxane - 0.001%
Roundup Ready-To-Use Weed & Grass Killer [2] EPA Reg: 71995-13 (11/6/1995)	Glyphosate - 1.55%; Polyoxyethylene alkylamine 0.36%; Water - 97.99 %; Antimicrobial Agent; 0.1%;
Roundup Weed & Grass Killer {1] Super Concentrate EPA Reg: 71995-18 (10/17/1996)	Glyphosate - 66.31%; Mon 59112 - 14.5% (TAM 7.25%, Phos Ester 2.93%, PEG 1.49%, DPG 1.38%, Water 1.45%); Water 19.36%; SAG - 0.01%
Roundup Weed & Grass Killer [1] Ready- To-Use EPA Reg: 71995-23 (5/20/1998)	Glyphosate 3.1%; Mon 59112 (polyoxethylene alkyl amine 0.25%, polyoxethylene alkyl phosphate ester 0.1%, Polyethylene glycol, 0.05%, dipropylene glycol 0.05%); Nonanoic acid 2%; Potassium Hydroxide 2.3%; Biocide 0.10%; silicone emulsion (dimethylpolysiloxane) 0.03%; Water 92.02%;
Isopropylamine Salt of Glyphosate (MON 0139, 62%)	Silicone Emulsion
	SAG 10 SAG 30

Table 11

Roundup Formulations potentially used by Plaintiffs - Chemicals within Glyphosate and Roundup Surfactants, Adjuvants and Co-formulants

Product Brand Name	Formulation(s)
CAS# 38641-94-0 (July 17, 1999)	Antifoam A Antifoam C Antifoam AF
	MON 59112 Surfactant
Roundup Weed & Grass Killer Ready-To-Use EPA Reg: 71995-32 (9/9/2002) (multiple formulations)	Glyphosate 3.23%; Mon 59112 0.5% (polyoxethylene alkyl amine 0.25%, polyoxyethylene alkyl phosphate ester 0.1%, propylene glycol 0.05%, dipropylene glycol 0.05%, water 0.05%); dipropylene glycol 0.05%; Nonanoic acid 2%; Potassium Hydroxide 2.3%; antimicrobial agent 0.10%; silicone emulsion (dimethylpolysiloxane) 0.03%; Water 91.89%;
Roundup Ready-to-Use Weed & Grass Killer III EPA Reg: 71995-33 (9/9/2002) (multiple formulations)	Glyphosate 3.23%; Mon 59112 0.5% (polyoxethylene alkyl amine 0.25%, polyoxyethylene alkyl phosphate ester 0.1%, propylene glycol 0.05%, dipropylene glycol 0.05%, water 0.05%); dipropylene glycol 0.05%; Potassium Hydroxide 1.94%; Ammonium Sulfate 2%; antimicrobial agent 0.10%; silicone emulsion (dimethylpolysiloxane) 0.03%; Water 90.22%;
	Glyphosate 3.23%; Polyoxyethylene alkyl amine 0.75%; antimicrobial agent 0.10%; water 95.92%
	Glyphosate 3.23%; Surfactant Blend 0.5% (Ethoxylated tallowamine 70%, glycerine 20%); Pelargonic Acid 2.0%; Potassium Hydroxide 2.3%; Ammonium Sulfate 2%; antimicrobial agent 0.10%; silicone emulsion (dimethylpolysiloxane) 0.03%; Water 89.86%;

Carcinogenic Substances in Roundup

Other than glyphosate, there is at least one additional known (confirmed) human carcinogenic substance identified as present in Roundup either as a formulation component or manufacturing reaction product that has been quantitively assessed by Monsanto. This reaction product (formaldehyde) is highly water soluble but also highly volatile with a boiling point of -2.2°F. The partial pressure of formaldehyde over water is 1.2 hPa and 1.3 hPa at 20 °C for 30 % and 50 % formaldehyde in aqueous solution, respectively. Thus, formaldehyde exposure can occur from direct inhalation.

- **Formaldehyde** is classified by IARC as a Class I human carcinogen and a probable human carcinogen (class B1) by the U.S. EPA. National Cancer Institute researchers have concluded that, based on human study data and lab research, exposure to formaldehyde may cause leukemia in humans, particularly myeloid leukemia. Peer-

reviewed studies have also documented increased rates of NHL among formaldehyde-exposed workers.[90]

- Monsanto previously performed an acute dose calculation in 1985. A document entitled "Potential formaldehyde exposure from wetcake, MON-0139 and Roundup® herbicide" was prepared by J.W. Worley on May 30, 1985.[91] In this study, Dr. Worley refers to the calculation and states that he used some "*completely arbitrary assumptions*" with only 1% of the formaldehyde assumed as escaping from the drum container when opened over a 15 minute period and "*only 1% of that is assumed to be inhaled by the worker*." With respect to the Roundup® herbicide, the *"calculated formaldehyde concentration in air was **2.8 PPM***." The study stated that the result was "*in the neighborhood of the allowed limits*" but also stated "*the ACGIH threshold limit value (TLV) is a **2 PPM ceiling**, a concentration that should not be exceeded even instantaneously*." However, the current NIOSH short-term exposure limit is **0.1 PPM**.
- It is also noteworthy that in 1995 a "*glyphosate centrifuge feed*" MSDS was created by Monsanto that revealed "*glyphosate centrifuge feed contains up to 1.3% formaldehyde*."[92] This is equivalent to 13,000 PPM.
- Formaldehyde (a Class 1 human carcinogen) has been demonstrated within human epidemiological studies to induce NHL.[93] Monsanto's material data safety sheet states, *"Formaldehyde is listed as a substance that 'may reasonably be anticipated to be' carcinogenic by the National Toxicology Program (NTP) in their Seventh Annual Report on Carcinogens. It is classified by the International Agency for Research on Cancer (IARC Monographs, Vol. 29). It is regulated by OSHA as a carcinogen (29 CFR 1910.1048)."* [94] The NIOSH 15-minute exposure ceiling limit is **0.1 PPM**. As stated above, formaldehyde is highly volatile with a boiling point of −2 °F and a vapor pressure < 1 atmosphere.

Simultaneous exposure to glyphosate and formaldehyde are of concern due to additive carcinogenicity. Typically, generally-recognized carcinogens with similar target endpoints (hematopoietic cancers) are, by definition, additive and should be considered in the

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[90] Wang, et al., "Occupational Exposure to Solvents and Risk of Non-Hodgkin Lymphoma in Connecticut Women," American Journal of Epidemiology, 2009 Jan 15; 169(2): pp. 176–185.

[91] MONGLY04267028-33.

[92] MONGLY00052410-13

[93] Wang, et al., "Occupational Exposure to Solvents and Risk of Non-Hodgkin Lymphoma in Connecticut Women," American Journal of Epidemiology, 2009 Jan 15; 169(2): pp. 176–185.

[94] MONGLY00029022.

overall carcinogen assessment of a product (such as Roundup).[95] The fact that other confirmed human carcinogenic substances are known to be present in trace amounts in Roundup (as noted in Monsanto's own documents) requires toxicological consideration. However, it is also noteworthy that these substances are not disclosed on the Roundup product label.

The U.S. EPA provides guidance on this issue as noted in the excerpt below from a generally-recognized toxicological U.S. EPA publication:[96]

> Epidemiologic studies, by their nature, are limited in the extent to which they can control for effects due to exposures from other agents. In some cases, the agent can have discernible interactive effects with another agent, making it possible to estimate the contribution of each agent as a risk factor for the effects of the other. For example, competing risks in a study population can limit the observed occurrence of cancer while additive effects may lead to an increase occurrence of cancer.

The U.S. EPA also offers guidance on the manner in which additive effects are required to be assessed:

> There may also be instances where the agent of interest is a risk factor in conjunction with another agent. For instance, interaction as well as effect-measure modification are sometimes construed to be confounding, but they are different than confounding. Interaction is described as a situation in which two or more risk factors modify the effect of each other with regard to the occurrence of a given effect. This phenomenon is sometimes described as effect-measure modification or heterogeneity of effect (Szklo and Nieto, 2000). ... When the effect of the exposure of interest is accentuated by another variable, it is said to be synergistic interaction. Synergistic interaction can be additive (e.g., hepatitis virus B and aflatoxin in hepatic cancer) or multiplicative (e.g., asbestos and smoking in lung cancer).

It is noteworthy that this is not a new or otherwise "novel" methodology. The "Health Effects of Toxic Substances"[97] reflects this view as a standard toxicological method:

> Additive effects imply that exposure to chemical carcinogens is additive over the lifespan of the organism. Carcinogenic substances are subject to the same bioaccumulation, transformation and excretion principles previously discussed. However, if there exists no threshold and a risk is assumed for any absorbed dose, then the probability of cancer induction would be additive.

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[95] Glyphosate (the primary chemical of concern) is noted to be present in the Roundup product (i.e., 2%) compared to other formulants and impurities such as POEA, formaldehyde and ethylene oxide.

[96] U.S. EPA, "Guidelines for Carcinogen Risk Assessment," U.S. Environmental Protection Agency Washington, DC, March 2005, EPA/630/P-03/001F

[97] M.J. Malachowski, "Health Effects of Toxic Substances," 1999, Second Edition, 0-86587-649-5.

Cancer or Tumor Promotion

Tumor promotion is a process in which carcinogenesis by various substances positively impacts the progeny of a single initiated cell(s) to survive and expand in number and to resist the process of normal cellular aging and death (known as apoptosis) and to continue on undergoing clonal malignant growth (known as tumor progression).

In the carcinogenicity study, George, J., et al., (2010),[98] glyphosate was demonstrated to have strong tumor-promoting activity. The study documented carcinogenic effects of glyphosate using a 2-stage mouse skin carcinogenesis model and proteomic analysis. The commercial formulation of Roundup Original (glyphosate 41%, POEA = 5%, Monsanto Company, St. Louis, MO, USA) was topically applied to the skin of mice with a body weight of 12-15 g. The glyphosate dose was 25 mg/kg body weight and was applied either two or three times per week.[99]

Proteomic analysis showed that 22 spots were differentially expressed (>2-fold) on glyphosate, 7,12-dimethylbrenz[a]anthracene (DMBA), and 12-O-tetradecanoyl-phorbol-1.3-acetate (TPA) application over untreated control. These results suggested that glyphosate has tumor-promoting potential in skin carcinogenesis and its mechanism seems to be similar to TPA.

Comparing the dosing in these mice to a hypothetical applicator at the AOEL of 0.1 mg/kg/day requires the consideration of body surface area, pharmacokinetics and physiological time.

Interspecies allometric scaling for dose conversion from animal-to-human is a method wherein the exchange of drug dose is based on normalization of dose to body surface area. This approach assumes that there are some unique characteristics of the anatomical, physiological and biochemical processes among species. The possible difference in pharmacokinetics/physiological time is accounted for by allometric scaling.

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[98] George, J., et al., "Studies on glyphosate-induced carcinogenicity in mouse skin: A proteomic approach," 2010, Journal of Proteomics 73, pp. 951 – 64.

[99] Somewhat similar to that of exposed sprayers mixing Roundup 2-3 times per week with dermal contact.

This method is frequently used in research for experimental purposes to predict an approximate dose on the basis of data existing in other species. **Table 12** contains an excerpt from Nair and Jacob, 2016, which uses data from FDA guidelines.[100],[101]

Table 12

Human equivalent dose calculation based on body surface area

Species	Reference Body Weight (kg)	Working weight range (kg)	Body surface area (m^2)	To convert dose in mg/kg to dose in mg/m^2, multiply by K_m	To convert dose in mg/kg to HED* in mg/kg, either Divide Multiply animal dose animal dose by	
Human	60		1.62	37		
Mouse	0.02	0.011-0.034	0.007	3	12.3	**0.081**

*HED: human equivalent dose

Applying the HED and 3% dermal absorption results in a reasonably similar dose to that sustained by a hypothetical applicator at the AOEL level of 0.1 mg/kg/day.

"Table 1" in the George, et al., study reveals that of the animals dosed only with the carcinogen 7,12-dimethybenz[a]anthracene (DMBA) at 52 ug/mouse, none of the 20 animals developed tumors. It should be noted that DMBA is a powerful carcinogen also found in cigarette smoke.[102] When also combined with glyphosate and applied to the skin (a single topical application of 50 mg/kg body weight per mouse), 40% of the mice developed tumors with an average of 2.8 tumors per mouse. The study demonstrated, to within 95% certainty, the carcinogenic potential of glyphosate as a powerful promoter in a 2-stage promotion model. The authors concluded in their results section that *"These results clearly indicate significant tumor promoting potential of glyphosate in mouse skin model of carcinogenesis."* It should also be noted that when the dose is factored by applying the human equivalent dose (HED) factor of 0.081 and a 3% dermal absorption factor, the glyphosate dose of 25 mg/kg body weight used in this study decreases to only 0.06 mg/kg human body weight which is less than the current "acceptable operator exposure level" (AOEL) for glyphosate (0.1 mg/kg body weight).

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[100] USFDA, "Guidance for Industry: Estimating the Maximum Safe Starting Dose in Adult Healthy Volunteers," 2005, Rockville, MD: US Food and Drug Administration.

[101] Nair AB, Jacob S., "A simple practice guide for dose conversion between animals and humans," 2016, J Basic Clin Pharma, Vol. 7, pp. 27-31.

[102] Lee, et al., "Polycyclic aromatic hydrocarbons present in cigarette smoke cause bone loss in an ovariectomized rat model," 2002, Bone, Vol. 30(6), pp. 917-23.

Monsanto has previously argued that the George study has been *"universally discredited"* and that my opinions are based on *"data that has been universally rejected as unreliable"* and that any demonstration of Roundup as a cancer "promoter" is inconsistent with the *"conclusions of all scientific panels and regulators that have reviewed it."* These are misleading characterizations. As shown below, even Monsanto's own Dr. Heydens stated that "*the surfactant in the formulation will come up in the tumor promotion skin study because we think it played a role there*."[103]

It is critically important to understand why the George study was not used by IARC, EFSA or EPA in formulating their published findings. The simple reason is that the George study was not a carcinogenesis bioassay. In other words, *the study was appropriately designed to determine whether glyphosate is a carcinogen.*

Defendant's assertion that the study has been *"universally discredited"* is a distortion and a fallacy. Nowhere in the peer-reviewed toxicological literature has this study been criticized on its merits. The George study was specifically designed using a well-known and established tumor promotion study design and it adhered faithfully to the boundaries of its objectives. As a tumor promotion study, it followed the generally-accepted study methodology without any deviations or errors.

The National Toxicology Program (NTP) recognizes the methodology as used in the George, et al., study as a well-known and generally-accepted procedure. The NTP states:[104]

"*Since the B6C3F1 mouse is commonly used in NTP carcinogenesis studies and much is known of its biology and response to chemical carcinogens, known initiators and promoters were used to compare the tumor response sensitivity of B6C3F1 mouse skin to that of two often-used responsive strains, Swiss (CD-1(R)) and SENCAR mice. The combination of 7,12- dimethylbenz(a)anthracene (DMBA) initiation and 12-O-tetra-decanoylphorbol-13- acetate (TPA) promotion was selected because this pair is routinely used to study tumorigenesis*."

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[103] Deposition of Dr. William F. Heydens, pages 150-151. Monsanto memos; MONGLY00997830 - MONGLY00997832.

[104] National Toxicology Program, "NTP Comparative Initiation/Promotion Skin Paint Studies of B6C3F1 Mice, Swiss (CD-1(R)) Mice, and SENCAR Mice", 1996, Natl Toxicology Program Tech Rep Ser. 1996 Feb;441: pp.1-201.

Even Monsanto's own toxicologists discern and differentiate the purpose of a "*tumor promotion study*" versus a "*carcinogenic potential of glyphosate*" study. In a memo[105] dated August 6, 2015, Dr. Heydens (a top Monsanto toxicologist) responded to a memo from Dr. Ashley Roberts (a consultant from Intertek). Dr. Roberts asked Dr. Heydens:

"*He [Dr. Keith Solomon][106] has asked if we need to give any consideration to exposures of formulants in the commercial product, at least in applicators? I was under the impression these were inert but reading a response this morning in the Ecologist makes it sound like it is the combination that is toxic!!!*"

Dr. Heydens (Monsanto) responded:

"*I think the short answer is no. The focus of this is what is the carcinogenic potential of glyphosate. That said, the surfactant in the formulation will come up in the tumor promotion skin study* ***because we think it played a role there.***"

The statement by IARC is consistent with the fact that the George, et al., study was not the appropriate methodology as used in the standard carcinogenesis animal bioassay methodology for carcinogenesis determination; rather, the methodology was that of generally-accepted tumor promotion methodology using a very low dose of a known carcinogen (DMBA) with and without glyphosate.[107]

The study was also criticized for its short duration of treatment (32 weeks). This is not consistent with standard animal bioassay methods which include dosing and observation for a longer duration. Thus, the shorter study design decreases the ability to detect tumor promotion. This criticism does not weaken the positive findings of the study.

The study was also criticized for "*no solvent control animals*." While it is standard practice to include a solvent-only treatment group in experimental design, the ethanol/acetone was the solvent and was present in five other treatment groups (100 mice). Those five

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[105] Monsanto memos; MONGLY00997830 - MONGLY00997832.

[106] Dr. Keith Solomon is "He" as per the video deposition of Dr. William Heydens (1-23-2017 at 12:06:17)

[107] "For more than 60 years, the chemical induction of tumors in mouse skin has been used to study mechanisms of epithelial carcinogenesis and evaluate modifying factors. In the traditional two-stage skin carcinogenesis model, initiation is accomplished by the application of a subcarcinogenic dose of a carcinogen. Subsequently, tumor development is elicited by repeated treatment with a tumor promoting agent." DMBA is typically used in such studies. DMBA produces "highly reproducible papilloma burden [which] is expected within 10–20 weeks with progression of a portion of the tumors to squamous cell carcinomas within 20–50 weeks." Abel, et al., "Multi-stage chemical carcinogenesis in mouse skin: Fundamentals and applications", 2009, Nature Protocols, Vol. 4(9): pp. 1350–1362.

groups did not show any papillomas. Ethanol/acetone compounds are well studied and commonly and generally used in similar study designs and have not been demonstrated to induce papillomas. Upon careful review of the study design:

- Zero of 20 mice in the glyphosate group developed papillomas (the glyphosate in this group was applied using the carrier solvent).
- Zero of 20 mice in the glyphosate (s) single application group developed papillomas (the glyphosate (s) in this group was applied using the carrier solvent).
- Zero of 20 mice in the glyphosate (t) three times per week application group developed papillomas (the glyphosate (t) in this group was applied using the carrier solvent).
- Zero of 20 mice in the DMBA (s) single application group developed papillomas (the DMBA in this group was applied using the carrier solvent).
- Zero of 20 mice in the t-phorbol acetate (TPA) group developed papillomas (the t-phorbol acetate (TPA) in this group was applied using the carrier solvent).

Thus, in total, 100 mice that received solvent (ethanol/acetone) - groups II, IV, V, VI, VII - were without any evidence of papillomas. Therefore, the reliability of this study with respect to the "*so called*" missing control group is not at issue.

The George study revealed that the Roundup product (41% glyphosate, POEA 15%) increased the incidence of tumors when combined with DBMA. The study demonstrated that glyphosate is capable of promoting tumors induced by an initiating chemical (DBMA). It is certain that Roundup, at a dose reasonably equivalent to that received by applicators, is a tumor promoter. In the George study, the well-known Group 1 carcinogen DMBA was administered to the mice.

To be clear: The George study was not designed to determine whether glyphosate itself is a carcinogen. This was not the objective of the study design. The George, et al., study was designed to determine whether Roundup promoted tumors.

The George study has been cited in at least 86 related scientific, peer-reviewed articles. There are no editorials or adverse criticisms within the peer-reviewed literature that I have found that are critical of this study as being "*unreliable*." Defendant's assertions in this regard are not supported by factual evidence.

The study revealed that when glyphosate was combined with DMBA (a powerful carcinogen found in cigarette smoke[108]) and applied to the skin, 40% of the mice developed tumors with an average of 2.8 tumors per mouse. Conversely, when the mice were dosed only with DMBA, none developed tumors. The study demonstrated, *to 95% statistical certainty*, the carcinogenic potential of glyphosate as a powerful tumor promoter in a 2-stage promotion model.

Thus, Defendant's attempt to criticize this study and my reliance upon it by asserting that determining whether or not glyphosate is a carcinogen was the focal point of the study is not accurate. Also, the criticism that the study was "flawed" due to no solvent group is not accurate and is misleading. There were actually 100 solvent carrier animals without a single papilloma.

Further, my report shows the transformation of the George study mouse dosage to a human equivalent dose (using the generally-recognized and accepted HDE methodology) is reasonable. The HED transformation shows that the dose in the George study was both reasonable and consistent with the documented dosage range of glyphosate applicators (AOEL). The animals received patch coverage of only 2 cm^2. Human applicators receive a substantially larger percentage of dermal impact than that of the mice in the George study. It should be noted that this is not the only promotion study I relied on.

Another peer-reviewed promotion study was published by Wang, et al. (2009).[109] The study data reveals that glyphosate elicits a B-cell-specific mutational mechanism of action in promoting carcinogenesis. The experimental evidence supports the epidemiologic finding regarding glyphosate's tissue specificity in carcinogenesis, *i.e.,* only increasing the risk for MM and NHL.

The Wang, et al., (2019) study provides the first in vivo evidence to support that glyphosate induces and promotes the disease progression to MM. The authors also revealed a B cell-specific mutational mechanism for glyphosate exposure that increases MM and NHL risk, providing a molecular basis for human epidemiological findings (Sawyer 10-31-2019 report).

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[108] Lee, et al., "Polycyclic aromatic hydrocarbons present in cigarette smoke cause bone loss in an ovariectomized rat model," 2002, Bone, Jun.30(6): pp. 917-923.

[109] Sawyer report pg. 61., Wang, L., et al., "Glyphosate induces benign monoclonal gammopathy and promotes multiple myeloma progression in mice," 2019, Journal of Hematology & Oncology, Vol. 12, p. 70.

Epidemiological studies have implicated glyphosate in the induction of multiple myeloma[110] (MM) via positive and statistically significant associations with glyphosate exposures. The Wang, et al. (2019) study[111] examined the impact of glyphosate in the pathogenesis of multiple myeloma. A distinctive characteristic of MM is that it is consistently preceded by MGUS[112], which is the increased production of the damaging M protein. The authors used specially bred mice[113] that are predisposed to developing a mouse equivalent to human MGUS, which then progresses to MM. This specially bred mouse model recapitulates many biological and clinical features of human MM, including increased serum immunoglobulin G (IgG), bone lesions and kidney damage.

The authors dosed the specially bred mice and normal wild-type mice with 1,000 mg/L glyphosate (~ 15 times the current ADI[114] allowed in the USA) in drinking water.

Following glyphosate dosing, the specially bred mice developed progressive hematological abnormalities and plasma cell neoplasms such as splenomegaly, anemia and high serum IgG[115]. Moreover, glyphosate caused multiple organ dysfunction, including lytic bone lesions and renal damage in these predisposed mice. Glyphosate-treated normal wild mice also developed some of the adverse conditions including benign monoclonal gammopathy with increased serum IgG, anemia and plasma cell presence in the spleen and bone marrow.

As a B-cell genome mutator, the substance called AICD[116] is known as a key pathogenic player in both MM and B-cell NHL. In the current study, glyphosate was found to increase the production of AICD in the spleen and bone marrow of both normal wild mice and the

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[110] Multiple myeloma is a type of blood cancer, wherein malignant plasma cells accumulate in the bone marrow. These malignant plasma cells then produce an abnormal antibody called M protein, which offers no benefit to the body and may cause tumors, kidney damage, bone destruction and impaired immune function. A defining characteristic of multiple myeloma is a high level of M protein in the blood (M spike).

[111] Wang, L., et al., "Glyphosate induces benign monoclonal gammopathy and promotes multiple myeloma progression in mice," 2019, Journal of Hematology & Oncology, Vol. 12, p. 70.

[112] Monoclonal gammopathy of undetermined significance (MGUS) is a condition in which an abnormal protein, known as monoclonal protein or M protein, is formed within your bone marrow and secreted into the blood.

[113] Bergsagel and colleagues generated a mouse model of MM (Vk*MYC) under the C57bl/6 genetic background with sporadic c-Myc activation in germinal center B cells, resulting in the development of benign monoclonal gammopathy, a mouse equivalent to MGUS, which then progresses to MM.

[114] The authors based this on the U.S. EPA chronic reference dose for an average adult weighing roughly 80 kg.

[115] The type of MGUS that most commonly leads to myeloma.

[116] Activation-induced cytidine deaminase (AICD)

specially bred mice. Thus, the glyphosate-induced damage occurred not only in the mice predisposed to MM but also in normal wild mice.

Most importantly, the study data reveals that glyphosate elicits a B-cell-specific mutational mechanism of action in promoting carcinogenesis. The experimental evidence supports the epidemiologic finding regarding glyphosate's tissue specificity in carcinogenesis, *i.e.,* only increasing the risk for MM and NHL.

The Wang, et al., (2019) study provides the first *in vivo* evidence to support that glyphosate induces and promotes the disease progression to MM. The authors also revealed a B cell-specific mutational mechanism for glyphosate exposure that increases MM and NHL risk, providing a molecular basis for human epidemiological findings.

Roundup and Glyphosate Genotoxicity

Genotoxicity is the ability of a chemical to cause damage to genetic information, *i.e.*, the DNA in cells, thereby causing genetic mutations that may lead to cancer. *There is strong scientific evidence that glyphosate is genotoxic and that glyphosate-based formulations such as Roundup cause oxidative stress capable of damaging DNA.*

Genotoxic Agents, Promotors and Inadequately Studied Chemicals

There are several such candidate substances in Roundup which are (a) unclassified by regulatory agencies and/or (b) substances for which only limited data or no peer-reviewed study data exists.

Such limitations make objective assessment very difficult as there is no single source of authority or regulatory guidance upon which to draw. For example, in a European Food Safety statement,[117] POE-tallowamine caused positive carcinogenic findings in a number of test systems. The consensus was that the likely causative basis was cytotoxicity (note that POEA compounds are banned in Europe and other countries outside the U.S.). There are also inconsistent results (depending on whose data is consulted) which note that an "unidentified" glyphosate-based formulation proved to be cytotoxic in bone marrow. However, tests of other formulations were negative.

Additionally, some substances only become carcinogenic when mixed with (or in the presence of) other substances which include formulation impurities. The interactive

[117] "Request for the evaluation of the toxicological assessment of the co-formulant POE-tallowamine," European Food Safety Administration, November 2015.

characteristics of such substances are not always clear. For instance, surfactant "C-6330" (an ethoxlylated fatty amine used by Monsanto) is noted as being *"very toxic to aquatic organisms."* The MSDS for this surfactant actually says very little of practical use as its composition is simply noted as "Proprietary." Such obfuscation of labelling chemical components merely serves to confound the assessment process as one does not (and cannot) know what is actually being assessed.

As previously noted, product ingredients can be examined individually when they are identified. However, it is critically important to note that when combined, these ingredients may have very different properties than the individual ingredients alone.

Oxidative Stress in Farmers Using Herbicides & PPE Protection**

Herbicides such as glyphosate, paraquat and 2,4-dichlorophenoxyacetic acid (2,4-D) have been reported to cause adverse side effects through production of reactive oxygen species. To determine the scope of such reports, Intayoung, et al., (2020)[118] investigated the effects of herbicide mixtures containing glyphosate, paraquat and 2,4-D in Thailand. The underlying hypothesis was that farmers who used these mixtures could induce oxidative stress leading to release of malondialdehyde (MDA, which is an oxidative stress biomarker) and glutathione (GSH). This prevents reduction of reactive oxidative species (ROS) to nontoxic substances in urine more than in a single-product use. The objective was to determine urinary MDA and GSH levels pre-work and post-work in Thai farmers using glyphosate, paraquat or 2,4-D in agricultural activity.

Ninety-three agricultural participants were randomly selected, the majority of whom were male. Most participants worked for at least 20-40 years. Fifty-six percent of participants used only glyphosate, 36.5% of participants used glyphosate with 2,4-D and 7.5% of participants used glyphosate and paraquat during their agricultural work.

Most farmers (42.9%) sprayed 4-6 tanks of herbicide per day and usually prepared herbicide dilution in water at a ratio of 200:1. Sixty-three percent of farmers worked on a farm for 1-5 hours per day. The interval time to collect urine samples before and after work was 21.84 ± 3.66 hours. Almost every participant wore masks, gloves and boots while working.

[118] Intayoung, U., et al., "Effect of Occupational Exposure to Herbicide on Oxidative Stress in Sprayers," 2020, Safety and Health at Work.

For urinary MDA level determination, participants were divided into three groups based on herbicide use: glyphosate, combined glyphosate and paraquat and combined glyphosate and 2,4-D. Results of urinary MDA levels showed pre-work urinary MDA levels were significantly higher in participants that used glyphosate and 2,4-D compared to those using only glyphosate. Post-work urinary MDA levels in participants using a combination of glyphosate and paraquat were significantly higher than those who work with only glyphosate, but there were no significant differences of urinary MDA levels between the pre-work and post-work sample among the three groups.

Although no significant differences were found in pre-work and post-work GSH content in each group of herbicide usage, GSH content in the urine of workers who used a combination of glyphosate and paraquat tended to decrease when compared with the other two herbicide groups. Linear regression was used to study the association between independent variables with results showing the MDA level in post-work urine samples significantly, positively associated with herbicide exposure intensity index and cumulative index.

Additionally, the authors found that wearing gloves during work can reduce the MDA level. Urinary GSH levels in post-work samples were not associated with all independent variables.

Overall, this study found a significant difference in urinary MDA level pre-work between farmers using glyphosate and those using combined glyphosate and 2,4-D. Farmers with a working history of prolonged use of many pesticides have been shown to have a significant increase in MDA level.

Studies Demonstrating Genotoxicity and Mutagenic Effects of Glyphosate

In the Bolognesi, et al., (1997) study,[119] analytical grade glyphosate (99.9%) and a Roundup formulation containing various surfactants and 30.4% glyphosate were tested in the same battery of assays to investigate and compare genotoxicity measurements. DNA damage was evaluated in terms of single-strand breaks and 8-hydroxydeoxyguanosine (8-OHdG) quantification in the liver and kidney. The chromosomal damage of the two pesticide preparations was evaluated *in vivo* in bone

[119] Bolognesi, Claudia, et al., "Genotoxic activity of glyphosate and its technical formulation," 1997, J. Agric. Food Chem. 45, pp. 1957-1962.

marrow of mice as micronuclei frequency and *in vitro* in human lymphocyte culture as SCE[120] frequency.

The study found significant oxidative damage of DNA. Glyphosate induced "large and significant" increases of 8-OHdG in the liver at 24 hours, but not in the kidney. Conversely, treatment with Roundup resulted in a significant increase of 8-OHdG over the control in the kidney but a nonsignificant increase in the liver.

A dose-dependent increase of cytogenetic damage, measured as SCE frequencies, was found in human lymphocytes treated with glyphosate over the control. Furthermore, a significant increment of the cytogenetic damage was evident in Roundup-treated lymphocytes compared to the glyphosate alone. The higher toxicity of Roundup resulted in the absence of mitotic cells above 0.33 mg/mL (333 PPM) and prevented the testing of higher doses. At the highest concentration of Roundup tested, the SCE/cell ratio was comparable to that obtained with a dose of glyphosate 10 times higher.

The *in vivo* bone marrow testing revealed an increase in micronuclei frequencies in all groups of treated mice. In addition, a significant reduction in the PCE/NCE ratio was evident in Roundup-treated mice showing target organ toxicity of the formulation.

The higher activity of Roundup in inducing toxic and genotoxic damage suggests that the co-formulants and/or surface active agents play a role in the potentiation of the effects of glyphosate.

Kang, et al., (2008)[121] found that in certain doses, glyphosate increases the micronucleus rate in the bone marrow cells of mice and causes sperm abnormalities and deformations in the heads of sperm. Roundup (41% glyphosate isopropylamine salt aqueous solution) was orally administered in doses that were determined by the LD_{50}:[122] low (1/8 LD_{50}= 580 mg//kg), medium (1/4 LD_{50}= 1,160 mg//kg) and high (1/2 LD_{50}= 2,320 mg//kg).

Using micronucleus testing,[123] Kang, et al., found that a 2,320 mg/kg dose of Roundup induced a marked increase in the bone marrow micronucleus rate in mice and exhibited

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[120] Sister chromatid exchange.

[121] Kang, JF, et al., "Study on mutagenesis induced by glyphosate in mice," 2008, Carcinogenesis, Teratogenesis & Mutagenesis, Vol. 20(3), pp. 227-320.

[122] LD stands for "Lethal Dose." LD50 is the amount of a material, given all at once, which causes the death of 50% (one half) of a group of test animals.

[123] Micronucleus testing of polychromatic erythrocytes in the bone marrow of mammals is a method of detecting chromosome damage and mutations in the body and chemical toxicity interfering with cellular mitosis.

a dose-dependent relationship. This shows that glyphosate has a significant mutagenic effect on the production of bone marrow cells in mice.

Also, the sperm abnormality rates in the glyphosate 1,160 and 580 mg/kg dose groups were significantly higher than in the negative control group ($P<0.01$, $P<0.05$). There was a dose-dependent relationship between exposure doses and sperm abnormality rates.

The authors conclude that glyphosate had a definite effect on both sperm counts and on the reproductive organs suggesting that glyphosate is mutagenic to the cells in mammals, damages sperm in mice and has the potential to cause mutations in male reproductive cells.

A study[124] on the role of agrochemicals in genotoxic damage used biomonitoring and environmental monitoring and examined biomarkers and other indicators of genetic damage in 30 pesticide applicators as compared to a reference sample of unexposed individuals. Exposures were noted to occur during the mixing and loading as well as the spraying of pesticide. The scientist behind the study noted that while applicators are known to work with a wide variety of chemicals in different formulations, glyphosate, in Argentine toxicological classification, is considered category IV; the lowest. Glyphosate can, therefore, be sprayed at less than 500 meters from homes and is cleared to be handled by applicators with minimal health protective measures.

The genotoxicity study revealed that, compared to the reference sample, pesticide applicators showed significant increase in DNA fragmentation, micronuclei formation and chromosome aberrations – chromatids and chromosome gaps, acentric fragments, chromosome and chromatids breaks and end reduplications. Further reporting by the applicators noted that 37% suffered from headaches and eye irritation during spraying and afterwards; 27% had respiratory allergies and/or skin reactions; 10% suffered digestive symptoms and 13% reported acute intoxication at least once after work.

Benedetti, et al.,[125] assessed genotoxic effects of pesticide exposure in soybean farm workers by evaluating human biomarkers buccal cells and peripheral leukocytes in the exposed and unexposed groups. Though this study did not exclusively examine effects

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[124] Aiassa, D. et al., “Evaluation of genetic damage in pesticides applicators from the province of Cordoba, Argentina,” 2019, Environmental Science and Pollution Research, Vol. 26(20), pp. 20981-20988. doi: 10.1007/s11356-019-05344-2. Epub 2019 May 21.

[125] Benedetti, D., et al., “Genetic Damage in Soybean Workers Exposed to Pesticides: Evaluation with the Comet and Buccal Micronucleus Cytome Assays,” 2013, Mutation Research- Genetic Toxicity and Environmental Mutagenesis, Vol 752, pp. 28-33. https://doi.org/10.1016/j.mrgentox.2013.01.001

of glyphosate alone, organophosphates were among the primary pesticides that workers were exposed to and which included glyphosate. The results of the study revealed that in exposed farm workers, there was resulting DNA damage (increased micronuclei, nuclear buds and binucleated cells) and cell death (condensed chromatin, karyorrhectic and karyolitic cells). Only 20% of the exposed farm workers group wore PPE; however, there was no difference in cell damage and cell death between exposed workers who wore PPE and those who did not wear PPE.

A study by Hutter, et al., has provided evidence to support genotoxicity effects in humans from spraying and application of organophosphates, "primarily glyphosate." In this study, pesticide-exposed workers not only sprayed pesticides but prepared and mixed the pesticides themselves and handled its disposal. A majority of the participants did not use PPE and lacked proper hand hygiene during eating and drinking.[126] Buccal cells were analyzed via buccal micronucleus cytome assay (BMCA) which reflects genotoxic effects including micronuclei, nuclear buds, broken eggs and binucleated cells as well as cytotoxic effects including condensed chromatin, karyorrhectic cells, karylytic cells and pyknosis. All biomarkers from BMCA revealed statistically-significant increased rates of nuclear anomalies in the pesticide-exposed group compared to the non-exposed group.[127] At 95% confidence interval, odds ratio for micronucleated cells was 3.1 (1.3-7.4) and odds ratio for pyknotic cells was 4.5 (2.5-8.2). The study concludes, "*Our results of the micronucleus cytome assays demonstrate impressively that the exposure to a mixture of agrochemicals may lead to long-term health consequences and suggests that pesticide users might have a higher risk of developing cancer*."

[126] Hutter, H-P., et al., "Cytotoxic and Genotoxic Effects of Pesticide Exposure in Male coffee Farmworkers of the Jarabacoa Region, Dominican Republic," 2018, International Journal of Environmental Research and Public Health, Vol 15, doi:10.3390/ijerph15081641

[127] Id.

Odds Ratio and 95% Confidence Intervals for Nuclear Anomalies in Pesticide-Exposed Workers (all statistically significant)
(from Hutter et al., 2018)[128]

Endpoints	OR	95% CI	*p*-Value
MN cells	3.098	1.297–7.404	0.011
Total MNi	2.524	1.219–5.226	0.013
Nuclear buds & broken eggs (BUD)	1.916	1.448–2.536	<0.001
Binucleated cells (BN)	1.412	1.207–1.650	<0.001
Condensed chromatin (CC)	1.306	1.054–1.618	0.015
Karyorrhexis (KR)	1.212	1.030–1.426	0.021
Karyolysis (KL)	1.286	1.132–1.462	<0.001
Pyknosis (PY)	4.536	2.517–8.173	<0.001
Basal cells	1.526	1.263–1.844	<0.001

Further Evidence of Genotoxic Effects

A recent study published in 2019 by Leite, et al., has provided further evidence to support the genotoxic effect of glyphosate (exposure via aerial spraying of organophosphate pesticides) by evaluating human biomarkers within (1) a community surrounded by transgenic soybean crops (such crops are generally bioengineered to allow for glyphosate spraying) and (2) the control group (group of children born and living in a community dedicated to family agriculture with biological control of pests).

The biomarker buccal micronucleus (with other nuclear abnormalities) was measured along with a comet assay analysis in the exposed and unexposed group to determine frequency of genetic (DNA) and cellular damage. The study showed significant differences between exposed and unexposed groups. All the following damages that were analyzed resulted in higher frequency in the exposed groups: micronucleus, increased binucleated, broken egg, karyorrhexis, karyolysis, pkynonsis and condensed chromatin.[129]

The study concluded that a greater and significant genotoxic and cytotoxic effect was observed in children exposed to pesticides compared to children unexposed to pesticides as evidenced by greater DNA damage to the exposed children. This is consistent with

[128] Id.

[129] Leite, S.N., et al., "DNA Damage Induced by Exposure to Pesticides in Children of Rural Areas in Paraguay," 2019, Indian Journal of Medical Research, Vol 150, pp. 290-296. DOI: 10.4103/ijmr.IJMR_1497_17

results from an earlier study done in Brazil which evaluated human exposure to pesticides in a similar manner in soybean farm workers.[130,131]

Genotoxic anomalies from exposure to pesticides may indicate the potential for cancer as these damages can induce mutations as well as other dangerous effects.

Figure 5 (from Leite, et al.) shows the increased frequency of cellular and DNA damage in the exposed group compared to the unexposed group.[132] The green highlight indicates exposed and unexposed groups.

[130] Id.

[131] Benedetti, D., et al., "Genetic Damage in Soybean Workers Exposed to Pesticides: Evaluation with the Comet and Buccal Micronucleus Cytome Assays," 2013, Mutation Research- Genetic Toxicity and Environmental Mutagenesis, Vol 752, pp. 28-33. https://doi.org/10.1016/j.mrgentox.2013.01.001

[132] Leite, S.N., et al., "DNA Damage Induced by Exposure to Pesticides in Children of Rural Areas in Paraguay," 2019, Indian Journal of Medical Research, Vol 150, pp. 290-296. DOI: 10.4103/ijmr.IJMR_1497_17

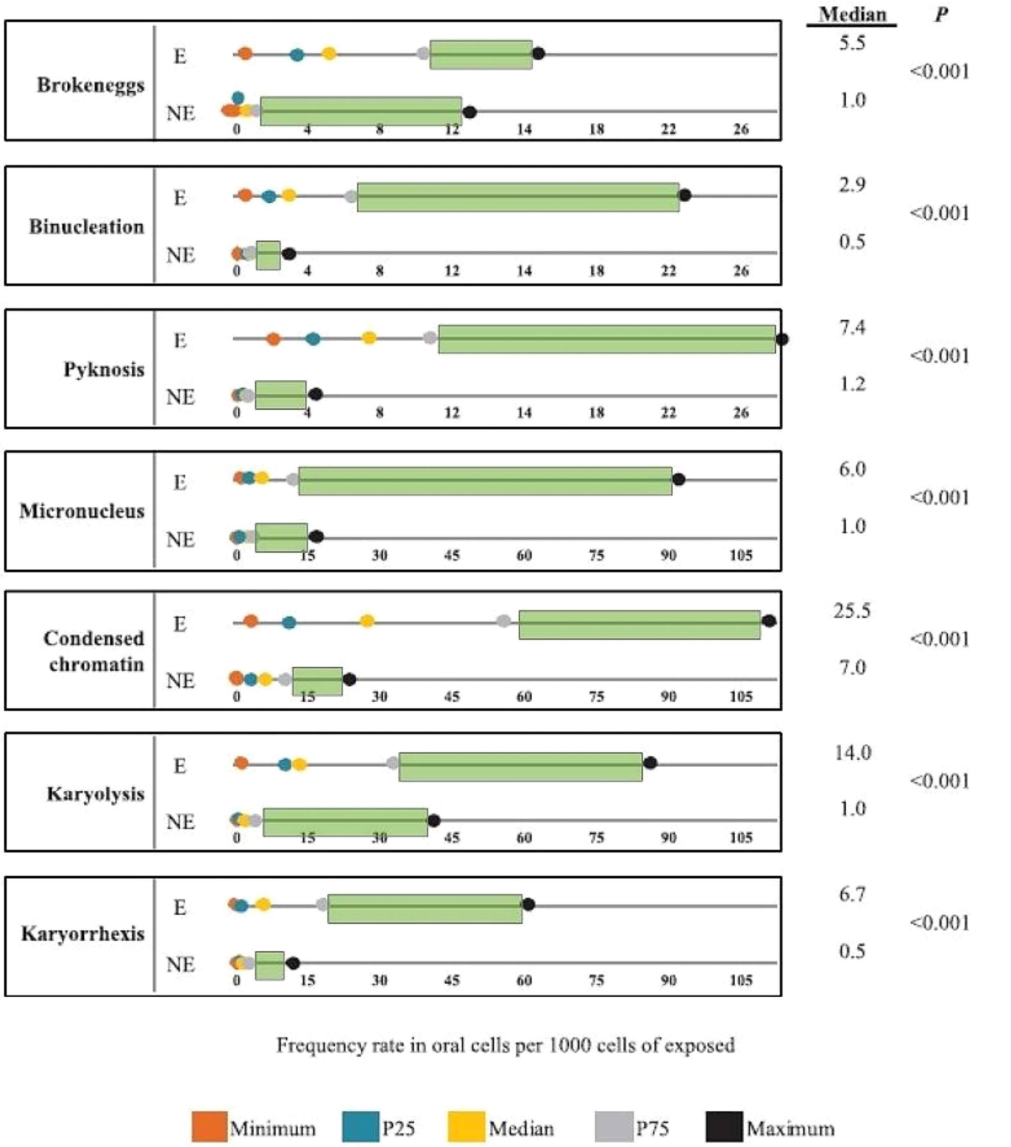

Fig. 1. Anomaly rate in oral cells per 1000 cells of exposed (E) (n=43) and not exposed (NE) (n=41). P25, 25th percentile; P75, 75th percentile. ▭ (shows difference between75th percentile and max).

Figure 5: Comparison of Anomaly Rate in Oral Cells between exposed and not exposed groups[133]

[133] Id.

A recent study by Wozniak et al.,[134] published in 2018, incubated human peripheral blood mononuclear cells (PBMCs) for 24 hours in the formulation Roundup 360 PLUS, glyphosate and its metabolite aminomethylphosphonic acid (AMPA). The study assessed the impact on DNA damage at concentrations of the tested chemicals ranging from 1 to 1000 µM. The Roundup formulation caused DNA damage (single strand breaks, double strand breaks, ALS formation, DNA lesions) even at concentrations as low as 5 µM and glyphosate and AMPA caused DNA lesions at concentrations of 250 µM and 500 µM, respectively. The amount of DNA damage caused by the chemicals increased from AMPA to glyphosate to Roundup 360 PLUS with Roundup causing DNA damage at concentrations 50 times lower than glyphosate. The DNA strand breaks induced at 10 µM application of Roundup were not repaired after incubation with PBMCs (incubation with PBMCs were shown to significantly repair DNA damage at 5 µM Roundup, 250 µM glyphosate and 500 µM AMPA). This underlined the point that glyphosate formulations are more toxic than glyphosate itself. The study also proposed that the damage occurred through oxidative reactions.

Published in 2020, Wozniak et al.,[135] further investigated the impact of DNA damage by glyphosate on DNA methylation level within selected gene promotors involved in proliferation, tumorigenesis and apoptosis. They incubated PBMCs for 24 hours in glyphosate at 0.5 µM, 10 µM and 100 µM. Results revealed a significant decrease of global DNA methylation with all glyphosate concentrations. Significant changes of methylation were found within the P21 gene promotor and TP53 tumor suppressor gene at the lowest glyphosate concentration. Significant gene expressions were revealed: decrease of P16 at all glyphosate concentrations, decrease of TP53 and increase of BCL2 at the highest concentration of glyphosate. In summary, there was decreased 5-mC level in PBMCs at all glyphosate concentrations which is comparable to environmental or occupational exposure (at the lowest 0.5 µM concentration). The results agreed with their previous findings in the 2018 study. Significant changes in methylation profiles of promotor genes involved in cellular metabolism were found. The significant upregulation of BCL2 expression could affect apoptosis induction.

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[134] Wozniak, E., et al., "The mechanism of DNA damage induced by Roundup 360 PLUS, glyphosate and AMPA in human peripheral blood mononuclear cells – genotoxic risk assessment," 2018, Food and Chemical Toxicology, doi: 10.1016/j.fct.2018.07.035

[135] Wozniak, E., et al., "Glyphosate affects methylation in the promoter regions of selected tumor suppressors as well as expression of major cell cycle and apoptosis drivers in PBMCs (*in vitro* study)," 2020, Toxicology in Vitro, Vol. 63.

Continuing their investigation, Wozniak et al.,[136] (published in 2020), further assessed the effects of aminomethylphosphonic acid (AMPA) alone on DNA damage. They incubated PBMCs for 24 hours in AMPA at 0.5, 10, and 250 µM to assess global DNA methylation, methylation in promoter regions of selected tumor suppressor genes and proto-oncogenes and expression profile of the indicated genes. Results revealed statistically-significant reduction of global DNA methylation AMPA concentrations of 10 µM and 250 µM. They demonstrated that, similar to glyphosate, AMPA significantly reduces global DNA methylation level in human PBMCs; however, it does not significantly alter the same gene expressions involved in regulation of cell cycle and apoptosis that glyphosate does. This demonstrates that glyphosate produces more damage than AMPA alone.

Another recent study of Suarez-Larios, et al., (2017) reveals a genotoxic mode of action for glyphosate pesticides. The investigation was undertaken by Suarez-Larios, et al.,[137] to determine whether or not exposure to pesticides would induce double-strand breaks (DSB) in cells (a lesion related to the formation of chromosomal rearrangements and increased leukemia risk). Of the eight pesticides tested (endosulfan, glyphosate, pentachlorophenol, permethrin, propoxur, AMPA, endosulfan lactone and paraoxon), four showed a significant effect on the number of cells with double-strand breaks. However, glyphosate and paraoxon (both organo-phosphates) showed the greatest increase in the number of cells with double-strand breaks. Further, it was determined that glyphosate and paraoxon reduced the number of viable cells in a dose-dependent manner; specifically, going from 100% cell viability to 70% with glyphosate. Not only did these two pesticides induce greater breakage, they also induced the phosphorylation[138] of KU80, a protein that participates in the c NHEJ recombinational repair pathway which is responsible for repair of the cells when double-stand breaks occur.

It was further noted in the study that these effects occurred at low concentrations in an acute treatment to cells in the laboratory setting. "*Effects over longer exposure in actual environmental settings are expected to produce cumulative damage if repeated events of recombination take place over time*." In other words, the more often a cell is damaged by glyphosate-induced breakage, the less likely the c NHEJ recombinational repair pathway will be able to repair it. Thus, the linear approach required by the U.S. EPA methodology

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[136] Wozniak, E., et al., "The selected epigenetic effects of aminomethylphosphonic acid, a primary metabolite of glyphosate on human peripheral blood mononuclear cells (in vitro)," 2020, Toxicology in Vitro, Vol. 66.

[137] Suarez-Larios, K., et al., "Screening of pesticides with the potential of inducing DSB and successive recombinational repair," 2017, Journal of Toxicology.

[138] Phosphorylation plays a critical role in the regulation of cellular processes.

is appropriate as the mode of action proposed by Suarez-Larios, et al., is not a threshold-based genotoxic mechanism. Other studies indicate that glyphosate can act as an endocrine disruptor[139] and has tumor-promoting activity.[140]

In vivo observations of human populations exposed to Roundup have revealed statistically significant outcomes demonstrating genotoxicity at low exposure levels[141] as well as *in vivo* studies of laboratory animals fed Roundup.[142] These studies challenge both animal and human systems providing *in vivo* doses of Roundup with resulting genotoxicity.

Furthermore, the exposure was to the Roundup product itself, not merely the chemical glyphosate. Additionally, these human cell studies present conditions with low dosing and concentrations and are, therefore, in no way extreme cases or otherwise inapplicable.

In Lioi, M.B., et al., (1998),[143] the authors studied the genotoxic activity of glyphosate[144] in *in vivo* cultures of bovine lymphocytes using chromosome aberration (CA) and sister chromosome exchange (SCE) frequencies as genetic endpoints and a variation of the G6PD[145] enzyme activity as a marker of changes in the normal cell redox state. The study found a statistically significant increase of CAs, SCEs and G6PD activity in glyphosate-exposed cultures when compared to controls.

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[139] Gasnier, C., et al., "Glyphosate-based herbicides are toxic and endocrine disruptors in human cell lines," 2009, Toxicology, Vol. 262, pp. 184 -191.

Thongprakaisang, S., et al., "Glyphosate induces human breast cancer cells growth via estrogen receptors," 2013, Food and Chemical Toxicology, doi: http://dx.doi.org/10.1016/j.fct.2013.05.057

[140] George, J., et al., "Studies on glyphosate-induced carcinogenicity in mouse skin: A proteomic approach," 2010, Journal of Proteomics, Vol. 73, pp. 951 – 964.

[141] Paz-y-Miño, C., et al., "Evaluation of DNA damage in an Ecuadorian population exposed to glyphosate*," 2007,* Genetics and Molecular Biology**,** 30(2).

Bolognesi, C., et al., "Biomonitoring of genotoxic risk in agricultural workers from five Colombian regions: Association to occupational exposure to glyphosate," 2009, Journal of Toxicology and Environmental Health, Part A, Vol. 72, pp. 986 -997.

[142] Peluso, M., et al, "32P-postlabeling detection of DNA adducts in mice treated with herbicide roundup," 1998, Environmental and Molecular Mutagenesis. Vol. 31(1), pp. 55 -59. DOI: 10.1002/(SICI)1098-2280(1998)31:1<55::AID-EM8>3.0.CO;2-A

[143] Lioi, M.B., et al., "Genotoxicity and oxidative stress induced by pesticide exposure in bovine lymphocyte cultures *in vitro*," 1998, Mutation Research, Vol. 403, pp. 13–20.

[144] Vinclozolin and DPX-E9636 were also included in this study.

[145] Glucose 6-phosphate dehydrogenase.

Glyphosate produced a significant increase in the percentage and frequency of aberrant cells (chromatid and isochromatid breaks). This clastogenic effect[146] was accompanied by a dose-dependent decreasing trend in cell proliferation.

In the cytoxicity study by Lioi, et al., (1998)[147] the authors analyzed CAs, SCEs, mitotic index (MI) and G6PD enzyme activity in human peripheral lymphocytes exposed to glyphosate *in vitro*.[148] Glyphosate induced a significant dose-related increase in the percentage and frequency of CAs; an increase of SCE frequency was also observed. A significant enhancement of G6PD enzyme activity was observed in the range of 8.5-51 µM glyphosate concentration. The study reported that the increase in the G6PD activity in the glyphosate-exposed lymphocytic cultures strongly indicated the induction of a pro-oxidant state of the cells as an initial response to exposure.

Duforestel M., et al., 2019,[149] stated that cancer rarely occurs in response to one risk factor. However, the known influence of glyphosate on estrogen-regulated pathway makes it a logical target of investigation in breast cancer research. The authors reference Thongprakaisang, et al., 2013, which reported that glyphosate induced the proliferation of human breast cancer cells via an impact on estrogen receptors. This observation is supported by several other studies demonstrating that glyphosate can affect the activity of estrogen receptor alpha (ERa) and certain phenotypes of ERa positive cells within breast cancer cell populations (Mesnage et al., 2017; De Almeida et al., 2018; Sritana et al., 2018).

Duforestel, et al., also presents evidence that glyphosate induces global DNA hypomethylation (i.e., overall decrease of 5-methylCytosine (5mC) in the epigenome) in non-neoplastic mammary epithelial MCF10A cells and contributes to tumorigenesis in a "two-hit oncogenic model." Their data also uncovers a specific DNA hypomethylation signature of genes (i.e., local DNA hypomethylation) related to the TET3 pathway that might be used as an epimark of glyphosate exposure.

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[146] Causing breaks in chromosomes which result in sections of a chromosome being deleted or rearranged.

[147] Lioi, M.B., et al., "Cytogenetic Damage and Induction of Pro-Oxidant State in Human Lymphocytes Exposed *In Vitro* to Glyphosate, Vinclozolin, Atrazine and DPX-E9636," 1998, Environmental and Molecular Mutagenesis, Vol. 32, pp. 39–46.

[148] Vinclozolin, atrazine and DPX-E9636 were also included in this study.

[149] Duforestel M., et al., "Glyphosate Primes Mammary Cells for Tumorigenesis by Reprogramming the Epigenome in a TET3-Dependent Manner," 2019, Front. Genet. 10:885. doi:10.3389/fgene.2019.00885

Glyphosate also triggered a significant reduction in DNA methylation as shown by the level of 5-methylcytosine DNA. Glyphosate triggered increased activity of ten-eleven translocation (TET). Combining glyphosate with enhanced expression of microRNA (miR) 182-5p associated with breast cancer induced tumor development in 50% of mice.

Culture of primary cells from resected tumors revealed a luminal B (ER+/PR-/HER2-) phenotype in response to glyphosate-miR182-5p exposure with sensitivity to tamoxifen and invasive and migratory potentials. Tumor development could be prevented either by specifically inhibiting miR 182-5p or by treating glyphosate-miR 182-5p-cells with dimethyloxallyl glycine, an inhibitor of TET pathway. Looking for potential epigenetic marks of TET-mediated gene regulation under glyphosate exposure, they identified *MTRNR2L2* and *DUX4* genes, the hypomethylation of which was sustained even after stopping glyphosate exposure for 6 weeks.

The low pressure but sustained DNA hypomethylation occurring *via* the TET pathway primes cells for oncogenic response in the presence of another potential risk factor, such as glyphosate. These results warrant further investigation of glyphosate-mediated breast cancer risk.

A study by Stur, et al., 2019,[150] analyzed the effects of Roundup and AMPA[151] on gene expression in triple negative BC cells. The authors identified gene expression changes in MCF-7 and MDA-MB-468 breast cancer cells after a short exposure time to low concentrations of Roundup Original and AMPA. The results showed that at low concentration (0.05% Roundup) and short exposure (48 hours), both cell lines suffered deregulation of 11 canonical pathways, the most important being cell cycle and DNA damage repair pathways. Enrichment analysis showed similar results except that MDA-MB-468 altered mainly metabolic processes. In contrast, 48 hour 10mM AMPA showed fewer differentially expressed genes but mainly related with metabolic processes indicating that that AMPA is less toxic than Roundup.

Their findings suggest that Roundup affects survival due to cell cycle deregulation and metabolism changes that may alter mitochondrial oxygen consumption, increase ROS levels, induce hypoxia, damage DNA repair, cause mutation accumulation and ultimately cell death. They concluded that both compounds can cause cellular damage at low doses

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[150] Stur, E., et al., "Glyphosate-based herbicides at low doses affect canonical pathways in estrogen positive and negative breast cancer cell lines," 2019, PLoS One. Vol. 14(7): e0219610. Published online 2019 Jul 11. doi: 10.1371/journal.pone.0219610

[151] AMPA is a metabolite of glyphosate.

in a relatively short period of time in these two models, mainly affecting cell cycle and DNA repair.

"…*we can conclude that Roundup, at much lower doses than the ones used in agriculture, was able to deregulate important intracellular pathways in ER+ and triple negative BC cell lines, showing that glyphosate's effect on cells is not exclusive to the ER pathway.*"

A 2018 study by De Almeida, et al.,[152] explored the effects of glyphosate, Roundup and another glyphosate-based herbicide in ER+ and ER- BC cell lines. Their results showed that these compounds can cause DNA damage at low concentrations and short exposure.

In Peixoto's 2005 study,[153] the potential toxicities of glyphosate and Roundup were tested in isolated rat liver mitochondria. The author determined the effects of Roundup and glyphosate on succinate-dependent respiratory indexes RCR and ADP/O of rat liver mitochondria. The data obtained clearly demonstrate the ability of Roundup to impair mitochondrial bio-energetic reactions. It was found that Roundup not only decreases the depolarization and repolarization amplitude induced by ATP, but also lengthens the "lag phase" prior to repolarization. Conversely, glyphosate alone does not show any relevant effect on the mitochondrial bioenergetics. Peixoto concluded that the observed alterations in mitochondrial bio-energetics caused by Roundup cannot be exclusively attributed to the active ingredient but may as well be the result of other chemicals (i.e., POEA) or due to the possible synergy between glyphosate and Roundup formulation products.

Prasad Study: Chromosomal Aberrations and Micronuclei in Bone Marrow Cells

Studies by Prasad, et al.,[154] examined the genotoxic effects of glyphosate as formulated in Roundup™ which contains the active ingredient, glyphosate (>41) SL (IPA salt) as purchased from Monsanto India, Ltd.

Chromosomal aberrations and micronuclei in bone marrow cells of Swiss albino mice were measured following a single intraperitoneal (*i.p.*) dose of Roundup™ with glyphosate

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[152] De Almeida et al., "Moderate levels of glyphosate and its formulations vary in their cytotoxicity and genotoxicity in a whole blood model and in human cell lines with different estrogen receptor status," October 2018, Biotech, Vol. 8(10).

[153] Peixoto, Francisco. "Comparative Effects of the Roundup and Glyphosate on Mitochondrial Oxidative Phosphorylation." Chemosphere, vol. 61, no. 8, 2005, pp. 1115–1122., doi:10.1016/j.chemosphere.2005.03.044.

[154] Prasad, et al., "Clastogenic Effects of Glyphosate in Bone Marrow Cells of Swiss Albino Mice," 2009, Journal of Toxicology, Volume 2009, Article ID 308985, doiaO.l 155/2009/308985.

doses levels at 25 and 50 mg/kg body weight. A positive control group received a single dose of the mutagenic carcinogen benzo(a)pyrene ((B(a)P) at 100 mg/kg body weight in a 0.2 ml dimethyl sulfoxide (DMSO) vehicle. Control and experimental animals received the same DMSO (*i.p.*) vehicle dosage.

Sixty (60) animals were divided into four groups of 15 animals each in two sets. The animals in Group I were used as a control group with DMSO only. The animals of Group II served as the positive control receiving the B(a)P. Animals in Groups III and IV received a single *i.p*. dose of glyphosate (diluted appropriately in DMSO) at either 25 or 50 mg/kg body weight, respectively.

Animals from all the groups were sacrificed at sampling times of 24, 48 and 72 hours and their bone marrow was analyzed for cytogenetic and chromosomal damage.

Glyphosate treatment significantly increased ($p<0.05$) chromosomal aberrations and micronuclei in bone marrow cells. Both treatments and time were compared with the vehicle control and were significantly different ($P<.05$). The cytotoxic effects of glyphosate were also evident as observed by a significant decrease in mitotic index (MI).

Review of Table 1 /Figure 2 reveals a consistent dose-response relationship among both the 25 and 50 mg/kg body weight doses at each time interval. It is also noteworthy that in the low (25 mg/kg body weight) dose group 72 hours after dosing, the rate of chromosomal aberrations was increased by a factor of 4.3 (7.76/1.8 = 4.3).

The authors concluded that the results indicate that glyphosate is clastogenic (a mutagenic agent) and cytotoxic to mouse bone marrow. The authors also state, "*For instance, the induction of DNA damage can potentially lead to adverse reproductive outcomes, the induction of cancer*..." With respect to reliability, the study also states *"Arguably, the most reliable genotoxicity evaluation for human health risk is conducted in mammals by the induction of chromosomal aberrations and micronuclei. In this regard, particular attention is focused on chromosomal aberrations because these are considered as early warning signals for neoplastic development."*[155]

A comparison of the dosing in the mice in the above study by Prasad, et al., (2009) to that of Roundup applicators exposed at the AOEL of 0.1 mg/kg body weight can be carried

[155] Bonassi, et al., "Are chromosome aberrations in circulating lymphocytes predictive of future cancer onset in humans? Preliminary results of an Italian cohort study," 1995, Cancer Genetics and Cytogenetics, Vol. 79, No. 2, pp. 133-135; Hagmar, et al., "Chromosomal aberrations in lymphocytes predict human cancer: a report from the European study group on cytogenetic biomarkers and health (ESCH)," 1998, Cancer Research, Vol. 58, No. 18, pp. 4117-4121 **in** Prasad, et al., "Clastogenic Effects of Glyphosate in Bone Marrow Cells of Swiss Albino Mice," 2009, Journal of Toxicology, Volume 2009, Article ID 308985, doiaO.I 155/2009/308985.

out using the generally-accepted Human Equivalent Dose (HED) methodology. This calculation is important in understanding the range of exposure dose in the animal as compared to a reasonable range of what a human may be exposed to. For example, some animal studies employ doses thousands of time higher than that experienced by actual human applicators of glyphosate.

Interspecies allometric scaling for dose conversion from animal-to-human is a method wherein the exchange of drug dose is based on normalization of dose to body surface area. The methodology requires the consideration of body surface area, pharmaco-kinetics and physiological time.

This approach assumes that there are some unique characteristics of the anatomical, physiological and biochemical processes among species. The possible difference in pharmacokinetics/physiological time is accounted for by allometric scaling.

This method is frequently used in research for experimental purposes to predict an approximate dose on the basis of data existing in other species. **Table 13** contains an excerpt from Nair and Jacob, 2016, which uses data from U.S. FDA guidelines.[156,157]

[156] U.S. FDA, "Guidance for Industry: Estimating the Maximum Safe Starting Dose in Adult Healthy Volunteers," 2005, Rockville, MD: US Food and Drug Administration.

[157] Nair AB, Jacob S., "A simple practice guide for dose conversion between animals and humans," 2016, J Basic Clin Pharma, Vol. 7, pp. 27-31.

Table 13
Human Equivalent Dose Calculation Based on Body Surface Area

Species	Reference Body Weight (kg)	Working weight range (kg)	Body surface area (m^2)	To convert dose in mg/kg to dose in mg/m^2, multiply by K_m	To convert dose in mg/kg to HED* in mg/kg, either Divide Multiply animal dose animal dose by	
Human	60		1.62	37		
Mouse	0.02	0.011-0.034	0.007	3	12.3	**0.081**

*HED: human equivalent dose

Applying the HED results in a dose of 2.0 mg/kg/body weight that is in a reasonable range of human dermal exposure compared to the AOEL of 0.1 mg/kg/body weight.

In the Prasad, et al., (2009) study, animals dosed at only 25 mg/kg body weight revealed a 4.3-fold increase in chromosomal aberrations at the 95% level of confidence ($p<0.05$).

It should also be noted that the test animals in this study underwent nearly 100% systemic absorption using the *i.p*. route of administration; thus, the application of the HED provides a reasonably accurate human dose estimate. The current acceptable operator exposure level (AOEL) for glyphosate is 0.1 mg/kg body weight. Thus, the Prasad, et al., (2009) study was not conducted at extreme (high) dose levels but rather, at dose levels not too far off from that encountered by glyphosate applicators.

Genotoxicity of Roundup, Glyphosate and POEA/Tallowamine (POEA) in Fish

In a study done on the effects of Polyoxyethylene Amine (POEA) on genotoxic, biochemical and physiological parameters of the freshwater teleost *Prochilodus lineatus*, a comet assay was used to analyze DNA damage in blood cells, indicating the genotoxicity of POEA at all concentration tested. The results of their study showed that POEA can cause effects such as hemolysis, DNA damage and lipid peroxidation, which are directly related to an imbalance in the redox state of the fish. Studies of acute exposure of P. lineatus to Roundup also found liver catalase activity inhibition. This suggests that both formulated Roundup and POEA interfere with the antioxidant defenses in fish. This study concluded that some of the effects observed after the fish were exposed to glyphosate-based herbicides may be related to the addition of POEA. The following

damages occurred: hemolysis, DNA damage, lipid peroxidation. They concluded exposure to POEA generates a condition of oxidative stress in fish.[158]

In a study by Marques, et al., titled "*Progression of DNA damage induced by a glyphosate-based herbicide in fish (Anguilla anguilla) upon exposure and post-exposure periods — Insights into the mechanisms of genotoxicity and DNA repair*" by Marques, et al., the authors aimed to improve the knowledge on the progression of DNA damage upon short-term exposure and post-exposure to Roundup. They evaluated DNA damage in hepatic cells via comet assays. They found that the liver cells of fish exposed to the lowest concentration of Roundup displayed significantly lower NSS_{FPG} levels[159] compared to the control. After absorbing the herbicide, the fish cells responded by enhancing its DNA repair capacity and/or mobilizing the antioxidant system as a response to ROS over-generation, reducing the cell vulnerability towards oxidative damage that was induced by the glyphosate. The results are evidence of a pro-oxidant status induced by Roundup and its potential to oxidatively damage DNA. In conclusion, they found **DNA repair** machinery was shown to be susceptible to inhibitory actions during the exposure period. The DNA repair enzymes seem to be susceptible to inhibitory actions associated with higher levels of Roundup constituents/metabolites.[160]

In a study conducted on the toxicity ranking and toxic mode of action for commonly used agricultural adjuvants, Ethoxylated tallow alkylamine was the most toxic compound tested.[161] A high toxicity after exposure to POEA had already been reported for several species such as tadpoles and green algae. The results of this study showed membrane damage after exposure to POEA and illustrates severe effects of DNA damage with the induction of bacterial SOS responses indicating possible genotoxicity for POEA.[162]

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[158] Navarro, Claudia D.C., and Claudia B.R. Martinez. "Effects of the Surfactant Polyoxyethylene Amine (POEA) on Genotoxic, Biochemical and Physiological Parameters of the Freshwater Teleost Prochilodus Lineatus." *Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology*, vol. 165, June 2014, pp. 83–90., doi:10.1016/j.cbpc.2014.06.003.

[159] Unclear what NSS is; FPG is a DNA-lesion specific endonuclease.

[160] Marques, A., et al., Progression of DNA Damage Induced by a Glyphosate-Based Herbicide in Fish (Anguilla anguilla) Upon Exposure and Post-exposure Periods--Insights into the Mechanisms of Genotoxicity and DNA Repair. Comp Biochem Physiol C Toxicol Pharmacol. 2014 Nov; 166:126-33. doi: 10.1016/j.cbpc.2014.07.009. Epub 2014 Aug 9.

[161] Other compounds tested include AE, tri-EO, EO FA and EO NP, and gamma-butyrolactone.

[162] Nobels, Ingrid, et al. "Toxicity Ranking and Toxic Mode of Action Evaluation of Commonly Used Agricultural Adjuvants on the Basis of Bacterial Gene Expression Profiles." *PLoS ONE*, vol. 6, no. 11, 18 Nov. 2011, doi:10.1371/journal.pone.0024139. https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0024139&type=printable

In a report done on the effects of surfactants on the toxicity of glyphosate, with specific reference to RODEO, possible mechanisms by which Roundup surfactants might exert biological effects or alter the toxicity of glyphosate included: decreasing surface tension, perturbing membrane permeability or transport function of membranes or other diffusion barriers and interacting directly with glyphosate to alter its disposition. The authors reference a study analyzing human poisoning cases by Sawanda, et al. (1998). This study indicated that the acute LD_{50} of POEA was "*less than one-third that of roundup and its active ingredient*". Martinez and Brown (1991) indicated that POEA by itself had a LD_{50} of 1-2 g/kg. POEA is more toxic in alkaline water than in acidic water, thus the relative potency of POEA with respect to glyphosate is pH dependent. In conclusion, POEA is substantially more toxic than glyphosate, and there is a lack of evidence on specific mechanisms of interactions between glyphosate and the surfactants.[163]

Recent Genotoxic Study of Pesticides (2019)

In Aiassa, D., et al., "Evaluation of genetic damage in pesticides applicators from the province of Cordoba, Argentina," 2019,[164] the authors conducted a descriptive-correlational study to determine if occupational exposure to pesticides constitutes a factor of genotoxic damage.

From the results of the many research studies from around the world that have provided scientific evidence of a positive correlation between exposure time, doses and high frequencies of these biomarkers, the authors found that the most common biomarkers used to evaluate the genotoxic effect in human populations occupationally exposed to pesticides are chromosomal aberrations (CAs), micronuclei (MN), sister chromatid exchanges (SCEs) and DNA fragmentation.

This study consisted of 52 individuals: 30 pesticide applicators and 22 male referents with no significant differences in lifestyle or diet between the two groups.[165]

The active ingredients of the most used pesticides were glyphosate, cypermethrin and chlorpyrifos. It was not possible to determine the damage caused by each individual

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[163] Diamond, G. et al., "Effects of Surfactants on the Toxicity of Glyphosate, with Specific Reference to RODEO." United States Department of Agriculture, 1997. https://www.fs.fed.us/foresthealth/pesticide/pdfs/Surfactants.pdf

[164] Aiassa, D. et al., "Evaluation of genetic damage in pesticides applicators from the province of Cordoba, Argentina," 2019, Environmental Science and Pollution Research, Vol. 26(20), pp. 20981-20988. doi: 10.1007/s11356-019-05344-2. Epub 2019 May 21.

[165] Of the six smokers in the exposed group, three smoked 10 cigarettes per day, one smoked 15 per day and two smoked 20 per day. Control group was non-smoking.

pesticide because the applicators were exposed to complex mixtures of agrochemicals. All applicators used ground-spraying machines. Twenty-three percent of pesticide applicators did not wear any personal protection equipment during spraying and mixing; 17% wore gloves, glasses and masks; 23% wore gloves only; 37% wore gloves and masks.

The genotoxicity tests performed in the pesticide applicators showed a significant increase in the mean of CAs, MN and DNA fragmentation relative to the reference group. The mean values for fragmentation of the DNA in the group of applicators was more than 10 times higher than those in the reference group (3,206 vs. 269). CAs, both with and without gaps, exhibited a statistically significant increase in the exposed group compared with the control group. Chromatid breaks and end reduplications were the two aberrations that showed statistically significant differences between the two groups.

The WHO's International Agency for Research on Cancer has re-reviewed glyphosate in their most recently published report and have not changed their opinion on the genotoxicity of glyphosate. They state:[166]

> *"The classification of glyphosate was supported by strong evidence that (i) glyphosate or glyphosate-based formulations are genotoxic based on studies in human cells in vitro and studies in experimental animals and (ii) glyphosate, glyphosate-based formulations, and major metabolite aminomethylphosphonic acid (AMPA) induce oxidative stress based on studies in experimental animals and studies in human cells in vitro."*

Mechanistic evidence relevant to key characteristics of carcinogens are supported by new studies with experimental animals and in human cells (e.g., Ghisi, et al., 2016; Santovito, et al., 2018, Wozniak et al., 2018).[167]

Modes of Action and Safety Considerations

Glyphosate can be applied both as a ground spray and as an aerial spray. It is used to modify plant growth, speed up the ripening of fruit, applied as a ground spray for peanuts

[166] International Agency for Research on Cancer. (2019). *Report of the Advisory Group to Recommend Priorities for the IARC Monographs during 2020-2024*. Retrieved from IARC WHO: https://monographs.iarc.fr/wp-content/uploads/2019/10/IARCMonographs-AGReport-Priorities_2020-2024.pdf

[167] Id.

and an aerial spray for sugarcane.[168] Glyphosate is also sprayed directly on wheat just prior to harvest as a consequence of a peculiar practice called *"browning"* or *"desiccating."*

Glyphosate is absorbed by the leaves and stems of the plant and readily translocated throughout. Specifically, glyphosate disrupts the shikimate acid pathway[169] by inhibiting the activity of a key enzyme (EPSP synthase) that is needed to form the essential amino acids.[170,171,172] The shikimate acid pathway is a crucial process in all higher-order plants. Thus, glyphosate will kill most plants. Glyphosate-resistant crops use an alternative EPSP enzyme and are, therefore, specifically genetically engineered to withstand extremely high levels of glyphosate without perishing. This metabolic process is also a crucial one in many microorganisms, but it is not utilized directly by animals or humans.

Throughout the years, Monsanto has advertised and promoted the safety of their Roundup products by claiming that the active ingredient, glyphosate, works by targeting an enzyme found in plants but not in people or pets.

However, recent evidence suggests that glyphosate may disrupt the essential shikimate process in bacteria, particularly the beneficial bacteria of the human intestinal tract. Additionally, glyphosate has been shown to sporadically cause potent inhibitions in the xenobiotic-metabolizing enzyme CYP2C9[173] which is responsible for biotransformation, metabolism and elimination of various toxic compounds from the body.[174]

A recent review by Samsel and Seneff (2013) hypothesized that glyphosate's known ability to disrupt the intestinal bacteria flora and to suppress a family of enzymes that play an important role in detoxifying harmful chemicals could be contributing to a rise in

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[168] Id.

[169] Williams, G. et al., "Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans," 2000, Regulatory Toxicology and Pharmacology, Vol.31, pp. 117 - 165.

[170] Boocock, M. R., "Kinetics of 5-enolpyruvylshikimate-3-phosphate synthase inhibition by glyphosate," 1983, FEBS Letters 154, pp. 127-133.

[171] Hollander, H., & Amrhein, N., "The site of the inhibition of the shikimate pathway by glyphosate," 1980, Plant Physiol 66(5), pp. 823-829.

[172] Schönbrunn, E. et al., "Interaction of the herbicide glyphosate with its target enzyme 5-enolpyruvylshikimate 3-phosphate synthase in atomic detail," 2001, Proc Natl Acad Sci USA Feb 13; 98(4), pp. 1376–1380.

[173] Abass, K., Turpeinen, M., and Pelkonen, O. "An evaluation of the cytochrome P450 inhibition potential of selected pesticides in human hepatic microsomes," 2009, Journal of Environmental Science and Health Part B, 44(6).

[174] Gueguen, Y. et al., "Cytochromes P450: xenobiotic metabolism, regulation and clinical importance," 2006, Ann Biol Clin (Paris) 64, pp. 535-548.

modern human diseases worldwide.[175] Glyphosate has also been demonstrated to be genotoxic and carcinogenic as discussed in detail.

Adverse Effects of Glyphosate on Human Gastrointestinal (GI) Microbiome**

As the most common broad-spectrum herbicide, glyphosate targets the key enzyme of the shikimate pathway, EPSPS (5-enolpyruvylshikimate-3-phosphate synthase). This enzyme synthesizes three essential aromatic amino acids (phenylalanine, tyrosine and tryptophan) in plants. However, the shikimate pathway is also found in many prokaryotes and in fungi. Thus, the widespread use of glyphosate may have unsuspected impacts on microbial communities – including the human GI microbiome.

Leino, et al., (2020)[176] proposed a bioinformatic method to predict the glyphosate sensitivity/resistance of organisms based on the type of EPSPS which is the biochemical target enzyme for glyphosate. The article offered a conservative estimate from results showing that 54% of species in the core human GI microbiome are sensitive to glyphosate.

The EPSPS enzyme synthesizes three essential amino acids in prokaryotes, plants and fungi. Although this pathway is absent in vertebrates, the shikimate pathway is important in microbes contained within the human GI microbiome. This methodology classifies EPSPS enzymes into four different classes with differential sensitivities to glyphosate based on presence and absence of amino known acid markers in the active site. This is useful to assess species that are putatively sensitive or resistant to glyphosate.

The dataset includes 890 sequences from species in the core human GI microbiome of which 54% are putatively sensitive to glyphosate (the study author's conservative estimate). It is also worth noting that this segment of the human microbiome represents approximately 20% of the total number of bacterial species in the GI.

Species containing class II EPSPS sequence are sensitive to glyphosate. A large portion of EPSPS proteins do not belong to any of the four known classes and are termed

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[175] Samsel, A. and Seneff, S., "Glyphosate's suppression of cytochrome P450 enzymes and amino acid biosynthesis by the gut microbiome: Pathways to modern diseases," 2013, Entropy (15), pp. 1416-1463.

[176] Leino L, et al., "Classification of the glyphosate target enzyme (5-enolpyruvylshikimate-3-phosphate synthase) for assessing sensitivity of organisms to the herbicide," 2020, Journal of Hazardous Materials.

"unclassified EPSPS." Further studies are needed to identify suitable amino acid markers that determine potential sensitivity of the unclassified EPSPS proteins to glyphosate.

EPSPS sequences of 890 strains from 101 common bacterial species in the human GI were analyzed. Results suggest that EPSPS sensitivity is conserved within bacterial species in the human GI such that 12-26% of bacterial species in the human microbiome might be sensitive and affected by glyphosate while 28.71% of species in the core microbiome are likely to be resistant to glyphosate. Meanwhile, 15.84% are unclassified or contain unclassified strains. Of the ten most frequent bacterial species in the core human GI microbiome, four species are resistant to glyphosate, four species are sensitive and two are unclassified.

Hence, a large portion of bacteria in the human GI microbiome are susceptible to glyphosate. Glyphosate intake may severely affect human GI microbiome composition. This may lead to a competitive advantage of bacteria resistant to glyphosate over sensitive bacteria which over time may lead to decreased bacterial diversity and modulate bacterial species composition in the GI. The assumption is that long-term exposure to glyphosate residues leads to dominance of resistant strains in the bacterial community while sensitive strains may become resistant to glyphosate via mutations in the EPSPS domain or acquisition of resistance gene via horizontal gene transfer.

Of toxicological significance is the fact that alteration of the metabolic pathways of glyphosate-resistant species can lead to subsequent toxic effects. More studies are needed to determine the impact of glyphosate on human GI microbiota including glyphosate residues in food, determination of effects of pure glyphosate and commercial formulations (surfactants) on microbiomes, and assessment of the extent to which the EPSPS amino acid markers predict bacterial susceptibility to glyphosate in vitro and real world scenarios.

Until more studies become available, it is clear that the potentially adverse effect of glyphosate on the human GI microbiome can lead to decreased pathogen defense, increased inflammation in the intestine and systemically contribute to adverse health effects.[177]

[177] Rueda-Ruzafa, L., et al., "Gut microbiota and neurological effects of glyphosate," 2019, Neurotoxicology, Vol. 75, pp. 1-8.

Glyphosate (Roundup) Formulations: Chemical and Physical Information

Glyphosate is the declared active ingredient (DAI) in Monsanto's Roundup herbicide products; however, it is only one ingredient in the formulation and *is almost never applied in isolated form*. Other substances (referred to as co-formulants) are added in order to modify the physicochemical properties, thereby improving the efficacy of the glyphosate-based formulation.[178,179,180] Examples of co-formulants are spreaders, compatibility agents, anti-foaming agents, drift retardants and surfactants.

The specific identities and the amounts of co-formulants in the herbicide formulations have largely been kept confidential because they are considered by Monsanto as proprietary data. Often, co-formulants are declared as "inert" as they do not act directly on the intended target*, i.e.,* the weed. Moreover, they historically have not been included in either toxicity tests of pesticides on mammals for the establishment of their acceptable daily intake (ADI) or in animal carcinogenicity studies.

Most glyphosate-based formulations (GBFs) contain the same three primary ingredients: (1) glyphosate salt, (2) co-formulants (e.g. surfactants) and (3) inert ingredients (e.g., "water").[181] Formulations differ from one another by the specific salt included in the formulation and the amount and type of surfactants, other co-formulants and inert ingredients. Glyphosate-based formulation ingredients can be examined individually; however, one must be mindful that the sum of these ingredients may have very different properties than the individual ingredients alone.

The salt of glyphosate in a GBF is comprised of an organic base combined with glyphosate. Glyphosate [N-(phosphonomethyl) glycine] is amphoteric (can act as either an acid or a base) and is practically insoluble in organic solvents.[182] Glyphosate as a weak acid has a hydrogen ion held to a phosphorous group by a weak electrostatic charge. By replacing this hydrogen ion with a different cation (organic base), herbicide

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[178] Defarge, N. E., "Co-formulants in glyphosate-based herbicides disrupt aromatase activity in human cells below toxic levels," 2013, Int J Environ Res Public Health. 13(3), pp. 264.

[179] Nobels, I. et al., "Toxicity ranking and toxic mode of action evaluation of commonly used agricultural adjuvants on the basis of bacterial gene expression profiles," 2013, PLoS ONE 6, p. 264.

[180] Haefs R. et al., "Studies on a new group of biodegradable surfactants for glyphosate," 2002, Pest Manag. Sci. 58, pp. 825–833.

[181] [redacted] Confidential draft. "Clustering glyphosate formulations with regard to the testing for dermal uptake," 2001. (Tab 15; see also MONGLY01839476 for draft of this document.)

[182] Williams, G. et al., "Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans," 2000, Regulatory Toxicology and Pharmacology, Vol.31, pp. 117 - 165.

manufacturers are able to make a more water-soluble glyphosate salt. Isopropylamine (IPA) is the organic base that is most commonly used in Roundup-formulated products.[183,184] This cation is also bound by a weak electrostatic charge and may not stay with the glyphosate acid; once it is added to water by the applicator, it can be easily replaced by other positively charged ions from the water.[185] Thus, the glyphosate that is working in the plant is usually not associated with the original salt.[186] The specific salt used in the formulation may not significantly impact herbicide performance. The glyphosate concentration in the final formulation will depend on the salt used as each salt has a different molecular weight. A lighter salt will result in a higher glyphosate concentration.[187] Several salt types have been used to formulate glyphosate products including isopropylamine (IPA), ammonium, sodium and potassium glyphosate salts[188] (see **Table 14**). Glyphosate isopropylamine salt is the one most commonly used in Roundup-formulated products[189] and used in all glyphosate-based products.[190]

[183] Id.

[184] [redacted] Confidential draft. "Clustering glyphosate formulations with regard to the testing for dermal uptake," 2001. (Tab 15; see also MONGLY01839476 for draft of this document.)

[185] Interactions between glyphosate and calcium salts found in water are the primary reason for adding AMS to the spray tank. (http://www.weeds.iastate.edu/mgmt/2001/glyphosateformulations.htm)

[186] [redacted] Confidential draft. "Clustering glyphosate formulations with regard to the testing for dermal uptake," 2001. (Tab 15; see also MONGLY01839476 for draft of this document.)

[187] The active ingredient concentration in a GBF is specified as a glyphosate equivalent or an acid equivalent (a.e.) referring to the free form of the acid. This allows for comparability between formulations.

[188] [redacted] Confidential draft. "Clustering glyphosate formulations with regard to the testing for dermal uptake." 2001. (Tab 15; see also MONGLY01839476 for draft of this document.)

[189] Giesey, J. P., Dobson, S., & Solomon, K. R., "Ecotoxicological risk assessment for Roundup herbicide," 2000, Rev. Environ. Contam. Toxicol. 167, pp. 35-120.

[190] U.S. EPA, "Registration eligibility decision-Facts: Glyphosate," 1993, United States Environmental Protection Agency, Prevention, Pesticides and Toxic Substances (7508W), EPA-738-F-93-011.

Table 14

Properties of Glyphosate and Common Salts of Glyphosate in Roundup[191]

Herbicidal Agent	Solubility in water (g/L)	MW (g/mol)	Molecular Formula
Glyphosate acid	**pH 1.9:** 10.5 **pH 7.0:** 157	169.07	$C_3H_8NO_5P$ or $HOOCCH_2NHCH_2PO(OH)_2$
Glyphosate Potassium salt	900[a]	207.16	$C_3H_7KNO_5P$
Glyphosate Ammonium salt	300[a]	186.11	$C_3H_{11}N_2O_5P$
Glyphosate Sodium salt	500[a]	191.06	$C_3H_7NNaO_5P$
Glyphosate Isopropylamine salt (IPA)	**pH 7.0:** 900 **pH 4.1:** 786	228.19	$C_6H_{17}N_2O_5P$ or C_3H_9N - $C_3H_8NO_5P$

[a] From "Managing Glyphosate. Performance of different salts and adjuvants." Grants Research and Development Corporation. GRDC Project code ICN00016.

Aside from the organic base and the salt used, the other major difference between glyphosate-based formulations is the inclusion of co-formulants. Some co-formulants are "pre-loaded" or included by Monsanto in the GBF while others, called adjuvants, are added by the end user to modify the herbicide to the particular situation in which it is being used.[192]

Adjuvants are not added to the GBF by the manufacturer mainly because different types of crops may require different types of adjuvant, *e.g.,* certain crops are sensitive to oils, some are difficult to wet, etc. Thus, herbicide manufacturers avoid limiting the application of a given herbicide to only one crop or situation.

As an example of adjuvant use, the addition of ammonium sulfate (AMS) and water conditioners have been shown to significantly improve weed control with glyphosate. Water in some regions contains excessive amounts of salts including calcium, magnesium, iron and sodium, and these salts bind to glyphosate and reduce its

[191] http://npic.orst.edu/factsheets/archive/glyphotech.html

[192] The terms "co-formulants" and "adjuvants" are sometimes used interchangeably in the literature. A fact sheet form Cornell University states, "A pesticide adjuvant is broadly defined as any substance added to the spray tank, separate from the pesticide formulation that will improve the performance of the pesticide. Sometimes adjuvants are more narrowly defined as a substance added to a pesticide mixture to improve its physical qualities and, hence, its effectiveness." http://psep.cce.cornell.edu/facts-slides-self/facts/gen-peapp-adjuvants.aspx

absorption and solubility. The sulfate component of AMS is negatively charged and will bind to positively charged salts so that they cannot reduce the activity of glyphosate. Other commonly used adjuvants include emulsifiers, dispersants, stabilizing agents, compatibility agents, buffering agents, anti-foam agents, spreader-stickers, drift retardants and surfactants.

Some GBFs may contain a greater percentage of co-formulants than glyphosate salt. These are listed simply as "Other Ingredients" on the label. For example, the label on Roundup Original Max herbicide, which contains a proprietary surfactant, reads

ACTIVE INGREDIENT

Glyphosate N (phosphonomethyl) glycine, in the form of its potassium salt	48.7%
OTHER INGREDIENTS	51.3%
	100%

The most commonly pre-loaded co-formulants used in herbicides are surfactants. Surfactants are complex chemicals that facilitate and accentuate the emulsifying, dispersing, spreading, wetting or other surface-modifying properties of aqueous solutions. For example, waxes on plant leaves are lipophilic and chemically non-polar and thus repel water while herbicides such as glyphosate are highly hydrophilic and chemically polar.

Adding surfactants will significantly increase how well glyphosate spreads on and enters leaf surfaces. A surfactant can also reduce the amount of glyphosate washed off of plants by rain. Surfactants in herbicides vary greatly in their nature and concentration and are added to increase the absorption rate of the acid into the plant's leaf and stem tissue. Sometimes a combination of surfactants is used in one glyphosate formulation. The most prevalently used surfactants in herbicides contain POEA (Polyoxyethylene alkylamine).

The co-formulants in a GBF (individually or in combination with one another) can have a profound toxicological effect on a non-target organism. Some of these co-formulants may synergistically attenuate the negative effects of glyphosate, or as in the case of surfactants which can increase dermal absorption, may simply increase glyphosate's systemic exposure. Surfactants, as well as other co-formulants, are particularly important with respect to a risk assessment and are, therefore, discussed in detail later in this report.

Roundup is offered in dry or aqueous formulations at various concentrations. Glyphosate is commonly formulated with water at 2.13 M (356 g/L free acid) or as an isopropylamine salt 480 g/L.[193] The ethoxylated tallowamine (POEA) surfactant in Roundup Classic is designated by Monsanto as MON 0818[194] with a concentration that is typically reported as approximately 15% of the formulation weight to volume or 150 g/L.[195,196,197,198]

Toxicological Considerations of Exposure and Dose

In assessing exposure, toxicologists examine how humans come into contact with chemicals, the amount of the chemical that enters the body (absorbed dose) as a result of contact and how these amounts change over time (pharmacokinetics). The goal of the exposure assessment is to quantify the amounts over various time periods. The quantitative expression of those amounts is referred to as dose. Thus, dose is the measurement needed to quantify a chemical's risk of toxicity. Therefore, the first goal of any exposure assessment is to objectively establish dose. With respect to human doses associated with NHL, the human epidemiological studies have used duration of exposure as the dose metric rather than blood or urine samples measuring glyphosate or its metabolite in units of mg/kg body weight.

Systemic Dose

When a person is exposed to a chemical such as glyphosate, the dose physically contacting the body is referred to as the "exposure dose." This is different from the "systemic dose" which enters the bloodstream and reaches various organs within the body. (For example, bone marrow where stem cells associated with the development of NHL are located).

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[193] Williams, G. et al., "Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans," 2000, Regulatory Toxicology and Pharmacology, Vol.31, pp. 117 - 165.

[194] Monsanto response to the concern of the Slovenian authorities on the composition of the Plant Protection Product MON 79376 (360 g/ 1 glyphosate) and the surfactant MON 59117 (CAS n ° 68478-96-6). MONGLY02817577.

[195] Id.

[196] Diamond, G., Durkin, P., "Effects of surfactants on the toxicity of glyphosate with specific reference to RODEO," 1997, Syracuse Research Corporation, SERA TR 97-206-1b.

[197] Giesey, J. P., Dobson, S., & Solomon, K. R., "Ecotoxicological risk assessment for Roundup herbicide," 2000, Rev. Environ. Contam. Toxicol. 167, pp. 35-120.

[198] Defarge, N. E., "Co-formulants in glyphosate-based herbicides disrupt aromatase activity in human cells below toxic levels, 2016, Int J Environ Res Public Health, Vol. 13(3), p. 264.

Systemic dose is typically only a portion of the exposure dose and is identified through pharmacokinetic (PK) or chemical disposition studies that can trace the fate of a chemical after it enters the body. Pharmacokinetic studies investigate the amount of a chemical absorbed by the body, how the chemical is distributed throughout the body to specific tissues, how the chemical is metabolized and finally, how a compound is excreted from the body. This is commonly known as ADME (absorption, distribution, metabolism and excretion).

ADME data is applied in conjunction with epidemiological and occupational exposure studies that have included biomonitoring and dosimetry for use in the human health risk assessment process. Thus, pharmacokinetic studies provide a necessary link between estimates of exposure, toxicity studies and estimates of human risk. It is, therefore, imperative that these studies are designed, conducted and interpreted accurately.

Monsanto Animal Study Characterizing Glyphosate Distribution & Excretion**

Brewster, et al., 1991[199] (a Monsanto company study) investigated the tissue distribution of glyphosate in Sprague-Dawley rats. A single oral dose of radiolabeled glyphosate (test material synthesized by Monsanto) was administered via oral intubation. Animals were administered 10.44 ± 0.09 mg glyphosate/kg body weight containing 1.42 ± 0.04 x 10^8 disintegrations per minute as determined by aliquots of dosing solution at the time of dosing.

Pharmacokinetic studies were performed on rat blood and tissue collected at various time points. Urine and feces were collected at 2 and 6.3 hours and at 24 hour intervals up to 168 hours post-administration. Tissue, urine, fecal and whole-body elimination were then analyzed.

The analysis results indicated that 36% and 51% of the administered dose was eliminated in urine and feces, respectively, over the seven-day observation period. Hence, the results indicate a minimum of 36% of the oral dose was absorbed from the GI tract (under the assumption that 100% of systemic glyphosate is only eliminated through the urine). Fecal elimination had greater impact on whole-body elimination than in urine; whole-body half-life was 2 days. The only tissues containing greater than 1% of the administered dose at any time period were small intestine, bone, colon and kidney. The major tissue depot

[199] Brewster, D.W., et al., "Metabolism of Glyphosate in Sprague-Dawley Rats: Tissue Distribution, Identification and Quantitation of Glyphosate-Derived Material following a Single Oral dose," 1991, Fundamental and Applied Toxicology, Vol. 17, pp. 43-51.

for glyphosate-derived radioactivity was the small intestine which contained greater than 34% of administered dose 2 hours after administration.

Bone contained significant amounts of radioactivity and about **5%** of the dose was associated with bone 6.3 hours post-administration. The small intestine, kidney, bone and colon were found to have the highest tissue-to-blood ratios. Glyphosate reached maximal tissue levels at 6.3 hours post-administration. Tissue levels declined rapidly with time in all tissues except bone. Metabolite characterization indicated more than 94% of extractable body burden was parent glyphosate. The only metabolite observed was detected in the colon 2 hours post-administration and was most likely AMPA which is known to be a microbial metabolic product of glyphosate.

The other Monsanto studies demonstrated that, at high levels, glyphosate produces a moderate inhibition of microsomal monooxygenases and it has little effect on peroxisomal β oxidation and GSH activity. Both urinary and fecal pathways thus provide important clearance mechanisms for glyphosate inasmuch as little metabolism occurs therein.

Less than 1.1% of administered dose remained associated with the bone and previous studies indicated no evidence of adverse effects to bone structure or function after prolonged exposures to glyphosate. Tissue-to-blood ratios significantly in excess of unity indicate tissue deposition.

Furthermore, the Brewster study found that urine and feces were equally important routes of administration and after 7 days, the total body burden (about 1%) of the dose administered was mostly in bone. At 168 hours (7 days) bone revealed a value of 1.06 + 0.04%.

Since dermal glyphosate exposure is the primary route of exposure contributing to systemic exposure in agricultural users, the assumption that distribution, metabolism and excretion are identical by IV and dermal routes of exposure leads to egregious errors in systemic dose calculations. **Figure 6** shows the results of tissue distribution from the Brewster, et al., study as published in *"Table 3."*

TABLE 3

TISSUE DISTRIBUTION (% ADMINISTERED DOSE) OF GLYPHOSATE DERIVED RADIOACTIVITY AT SELECTED TIME INTERVALS AFTER ORAL ADMINISTRATION OF 10 mg [^{14}C]GLYPHOSATE/kg BODY WEIGHT[a]

	Hours after administration				
Tissue/organ[b]	2	6.3	28	96	168
Abdominal fat[c]	0.15 ± 0.07	0.16 ± 0.02	0.15 ± 0.13	<0.02	<0.02
Blood[c]	0.38 ± 0.04	0.33 ± 0.00	0.06 ± 0.03	<0.02	<0.02
Bone[c]	2.03 ± 0.13	4.69 ± 0.22	2.72 ± 0.49	1.69 ± 0.04	1.06 ± 0.04
GI contents	51.33 ± 1.70	49.23 ± 0.15	7.03 ± 0.33	0.09 ± 0.02	0.06 ± 0.05
Colon	0.73 ± 0.45[d]	1.29 ± 0.40	0.20 ± 0.03	0.02 ± 0.00	<0.02
Carcass	3.30 ± 0.10	5.94 ± 1.16	2.40 ± 0.21	1.12 ± 0.19	0.91 ± 0.13
Kidney	0.73 ± 0.07	1.29 ± 0.08	0.13 ± 0.01	<0.02	<0.02
Liver	0.12 ± 0.05	0.17 ± 0.01	0.12 ± 0.01	0.06 ± 0.02	0.02 ± 0.00
Sm. intestine[e]	34.34 ± 2.30	18.48 ± 1.10	0.51 ± 0.01	0.05 ± 0.02	0.02 ± 0.01
Stomach	0.11 ± 0.03	0.13 ± 0.02	<0.02	<0.02	<0.02
Testicular fat[c]	0.39 ± 0.25	0.27 ± 0.11	0.02 ± 0.03	<0.02	<0.02
Total body burden	91.21	76.04	10.94	1.91	1.16

[a] Mean ± SEM of three to four animals.
[b] Less than 0.02% of the applied dose was found in the brain, heart, lungs, spleen, and testes at each time point.
[c] Abdominal fat, blood, bone, and testicular fat were estimated to be 5.5, 8, 8, and 5.5% of the body weight, respectively.
[d] The colon of one animal contained less than 1% of the administered dose.
[e] Tissue washed with saline. Data represent that activity associated with tissue and not intestinal contents.

Figure 6: "Table 3" from Monsanto-sponsored Brewster study (1991)

Human Biomonitoring and Glyphosate Exposure**

Owing to a paucity of relevant scientific data and ethical considerations, most toxicological assessments of human glyphosate exposure are necessarily based upon dermal contact of applicators. Indeed, the vast majority of studies are restricted to this circumstance. Thus, other exposure routes conducted using human experimental studies of inhalation and direct ingestion do not exist. This section briefly reviews alternate routes of exposure, recent studies exploring these conditions and the results of different types of biomonitoring as well as potential NHL impacts.

Human Glyphosate Excretion in Urine - Lower than Found in Animal Studies**

Zoller, et al.,[200] conducted a study to determine the fraction of glyphosate and AMPA excretion in urine after consuming regular food with glyphosate residue to estimate dietary glyphosate exposure. The study was designed by administering glyphosate via a test meal to 12 participants (6 male, 6 female) after a two-day wash-out period followed by a two-day urine sampling period.

The study methodology was scientifically pragmatic. An initial urine sample was collected shortly before the test meal, then participants were instructed to urinate regularly once every 1.5 hours to obtain enough data points during the first 6 hour post-glyphosate consumption. The test meal was a homemade falafel dish; the serving contained 196.8 µg of glyphosate and 1.67 µg of AMPA. The food was not spiked with glyphosate or AMPA. Both substances were present as residues in the chickpea flour used.

Glyphosate concentration prior to the meal administration was below 0.1 ng/ml for all participants. Half-life was approximately 9 hours for male and female participants. Mean sampling duration was 43.5 hours.

The results revealed median urinary excretion at 0.91% (mean 0.95%) of administered glyphosate dose for all participants. The study authors concluded that it is reasonable to assume that urine levels indicate approximately 1% of dietary glyphosate exposure. Thus, the mean 0.91% urinary excretion was 22 times lower than reported in animal studies which showed 20% excretion. However, animal studies were administered a dose by gavage and not by feeding; thus, absorption might be lower. It is important to note that the animal studies received much higher doses per kg body weight which could alter the pharmacokinetics. Furthermore, the low urinary excretion level determined in this study suggests that intake estimations calculated from human urine data systematically underestimate exposure.

In a separate study/Ph.D. thesis, Faniband[201] conducted human experimental exposures to pesticides to validate the exposure biomarkers in urine via LC-MS/MS quantification. Subjects observed a fasting period of two hours before and two hours after oral dose. A pre-exposure urine sample was collected from subjects before all experiments. Subjects

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[200] Zoller, O., et al., "Urine glyphosate level as a quantitative biomarker of oral exposure," 2020, Int. J. Hyg. Environ. Health, Vol. 228, 113526.

[201] Faniband, M., "Human Exposure Biomarker of Some Commonly Used Pesticides," Ph.D. Thesis, Lund University, Faculty of Medicine, Lund, Skaner, Sweden, 2020.

were administered a single oral dose of glyphosate, equivalent to 50% of the ADI 0.5 mg/kg/body weight per day for glyphosate, in the form of spiked organic juice.

The results of this study showed dose recovery of between 1-6% in urine excreted as parent glyphosate; half-life estimation was between 6-9-hours. Thus, dose excretion in urine was much lower compared to prior animal studies (10-30%).

Note: This study only had 2-3 subjects so results may vary for a larger sample size. Additionally, inhalation exposure to pesticides was not controlled. However, this vastly lower recovery of urinary glyphosate is highly consistent with Zoller, et al., findings.

Risk Characterization Using New 1% Urinary Glyphosate Excretion in Humans**

Connolly, et al., (2020)[202] evaluated glyphosate exposure using human biomonitoring data (urine samples) to relate internal glyphosate concentrations to health-based guidance values. However as noted herein, recent studies suggest human glyphosate excretion fraction in urine (unchanged) could be as low as 1% as outlined in preceding section(s). These are significant findings with direct outcomes impacting quantitative significance of urinary glyphosate and AMPA as established exposure biomarkers for glyphosate and exposure as well as risk extrapolations based upon human biomarkers.

It is important to note that prior animal-derived excretion rates suggested that there were no health concerns in relation to glyphosate exposure when compared with the European Food Safety Authority's acceptable daily intake (ADI). However, as noted above, recent human metabolism data reports a urinary glyphosate excretion rate of 1% or less. What happened to the other 99%? This is a serious toxicological concern.

Hence, the study authors' objective was to outline gaps in current scientific knowledge. Given glyphosate's current ubiquitous presence in our culture, it is highly appropriate to propose recommendations for sampling strategies to inform future studies investigating population exposures to glyphosate.

From review of the toxicological literature, average urinary glyphosate concentrations reported for farmers and horticulturists ranged from 1.35 µg/l to 3.20 µg/l with maximum values ranging from 10 µg/l to 233 µg/l. Therefore, occupational exposures in some settings may be as much as 100 times higher than previously assumed.

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[202] Connolly, A., et al., "Human Biomonitoring of Glyphosate Exposures: State-of-the-Art and Future Research Challenges," 2020, Toxics, Vol. 8(6), pp. 1-18.

Utilizing the most recent 1% urinary excretion mean urinary glyphosate concentration in workers in pesticide manufacturing would indicate systemic dose of approximately 10% of the AOEL with maximum urinary glyphosate concentrations 5.5 times the AOEL limit. This represents a significant excess. Non-occupational glyphosate exposure types varied in the study.

- In the Mills, et al., study of an older adult population (more than 50 years old), the mean urinary glyphosate concentration was 0.314 µg/l.
- The McGuire, et al., study of lactating women found a mean urinary glyphosate concentration of 0.28 µg/l; maximum concentration was 1.93 µg/l.
- The Curwin, et al., study of farm and 'non-farm' families investigating take-home pesticide exposure found mean (geometric mean) urinary concentrations of 1.4 µg/l, 1.2 µg/l and 2.7 µg/l, respectively for father, mother and child with a maximum concentration of 9.4 µg/l.
- Faniband, et al., and Zoller, et al., both reported urinary excretion of ingested glyphosate as low as 1% instead of 20% as observed from animal studies.

The lower excretion findings have numerous and significant impacts on all HBM-based (human biomonitoring) dose extrapolations. For example, the finding suggests a 20-fold higher glyphosate intake for human populations than previously assumed based on urinary glyphosate data of animals. When recalculating exposure, upper-bound urinary glyphosate concentrations in several non-occupational populations indicate intakes that could represent 5%, 6%, 53% and 87% of the ADI.

It is important to note that these low urinary excretion levels considerably diminish the established margin of safety for glyphosate exposure in the general population (as well as potentially-exposed sub-populations).

Controlled Dermal vs. Inhalation Residential Applicator Urine Glyphosate Levels**

As previously noted, dermal contact is not the only route of glyphosate exposure. Pierce, et al., (2020)[203] conducted a study evaluating inhalation and dermal exposures in non-occupational individuals exposed to Roundup® mixtures (used concentrate containing 50.2% glyphosate) and urinary glyphosate levels following heavy residential consumer application of GBH. Sampling was done while Roundup® concentrate was mixed by the applicator and subsequently sprayed using commercially-available backpack sprayers made by the same manufacturer in a manner consistent with product instructions.

Participants were divided into two groups: one for dermal exposure, the other for inhalation exposure. The dermal group applicators wore their own shorts, t-shirts, socks and athletic shoes, which was believed to be consistent with typical apparel worn by a residential consumer applicator on a warm day. (Study was conducted in July 2019 in Monee, IL). The dermal group also wore half-face respirators equipped with OV/AG/P100 cartridges. The inhalation exposure group applicators wore hooded Tyvek coveralls but shoes were not covered. Chemically-resistant gloves were provided but no respirators.

The duration of exposure simulation was 100 minutes to conform with the minimum air sampling duration specified within OSHA Method PV2067 (which is expected to be longer than typical residential consumer-use duration). When the backpack was empty, it was refilled and mixed and the process was repeated for a total of four mixing and spraying events per applicator in the 100 minute sampling period. Following exposure simulation, applicators washed their hands with soap and water. Urine samples were collected from participants 30 minutes prior to application and again at 3-, 6-, 12- and 24 hours after completion of application. An additional urine sample was collected 36 hours post-application for the dermal exposure group due to possible delays in absorption.

The study findings were highly revealing. Generally, urinary glyphosate levels were highest in samples collected 3 hours post-application with the exception of two subjects with peak urinary levels at 6 hours post-application (one in the inhalation exposure group and one in the dermal exposure group) and one subject in the dermal exposure group who peaked at 24 hours post-application. **Figure 7** presents graphs of urinary glyphosate concentrations for the inhalation (a) and dermal (b) groups over the sampling period.

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[203] Pierce, J.S., et al. "Pilot study evaluation inhalation and dermal glyphosate exposure resulting from simulated heavy residential consumer application of Roundup®," 2020, Inhalation Toxicology, International Forum for Respiratory Research.

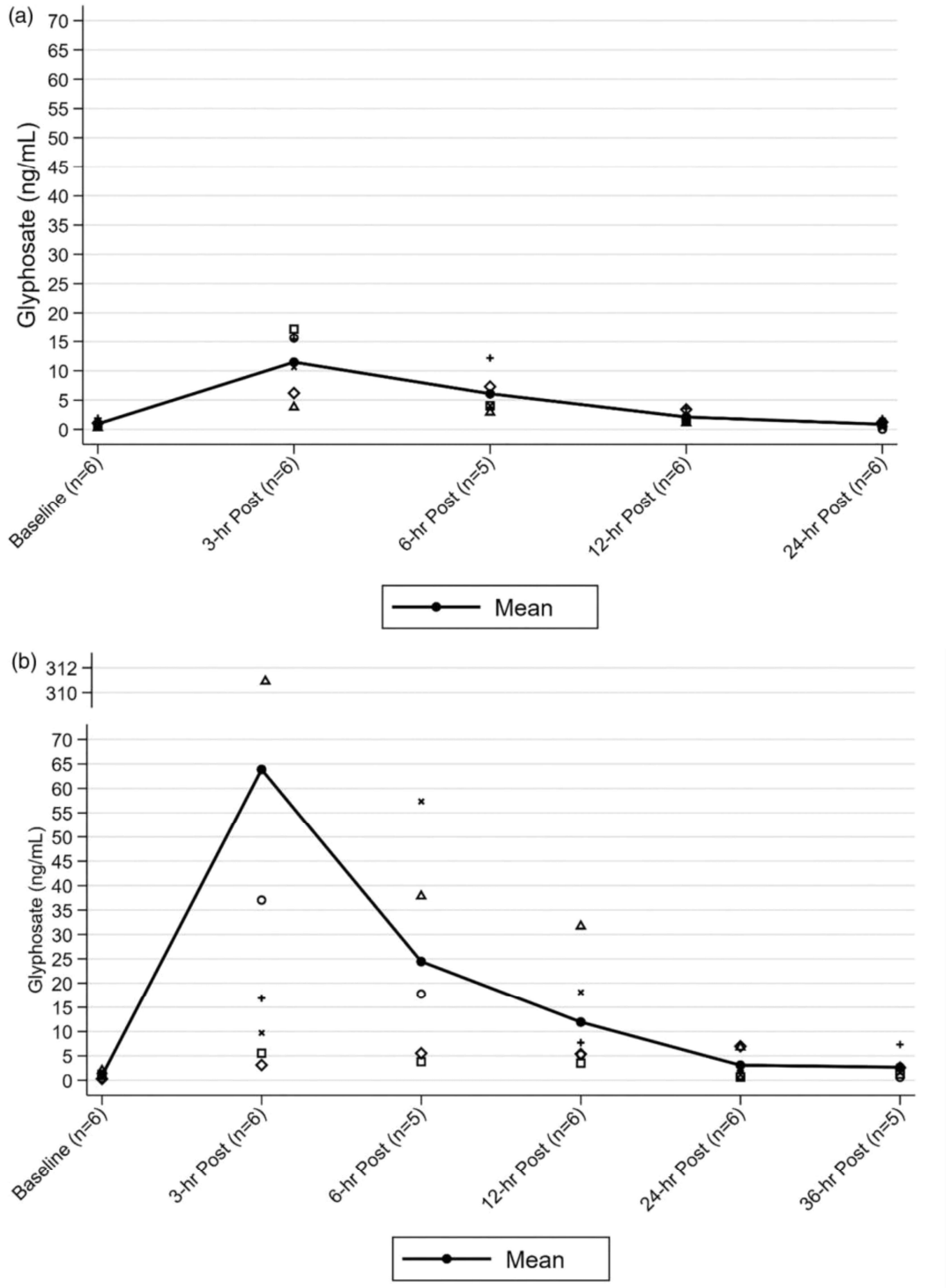

Figure 7: Urinary glyphosate concentrations for (a) inhalation group and (b) dermal group.

With regard to peak urinary glyphosate results, concentrations ranged from 3.79-17.23 ng/ml for the inhalation exposure group and 5.55-310.91 ng/ml for the dermal exposure group. Excluding the 310.91 ng/ml as an outlier, the highest urinary glyphosate level measured in the dermal exposure group was 57.36 ng/ml.

For both exposure groups combined, urinary glyphosate levels were significantly elevated relative to baseline until 24 hours post-application. This held true when the model was run separately for the dermal group. However, for the inhalation group, urinary glyphosate levels were significantly elevated relative to baseline until 12 hours post-application. Overall, geometric mean urinary glyphosate levels were higher in the dermal exposure group but not statistically significant. Airborne glyphosate concentrations ranged from 0.0030 mg/m^3 to 0.0075 mg/m^3 with an overall mean of 0.0047 mg/m^3. The mean concentration of glyphosate for each applicator's four dermal patch samples ranged from 0.04 $\mu g/mm^2$ to 0.25 $\mu g/mm^2$. Generally, the highest concentrations were measured on the right shin followed by the left shin.

The strengths of this study include well-defined mixing and application protocol that simplifies interpretation of the toxicokinetics of glyphosate. The standardized mixing and application procedures with continuous application over a fixed duration and fixed volume of a single type of GBH with a known concentration was used; no other studies have controlled for all of these variables. The lack of statistical significance in glyphosate concentration between the two exposure groups is likely due to small sample size as well as the fact that the inhalation exposure group did not have their shoes covered. Many applicators of both exposure groups reported their shoes were wet following application. So individuals in the inhalation group may have been incidentally dermally exposed through their feet.

Overall, the results of this study were consistent with previous studies showing that glyphosate is quickly eliminated from the body within 24 hours following application. The charts shown in **Figure 7** reveal well-ordered results demonstrating glyphosate urinary concentrations over the time period sampled at baseline and time points post-application.

It is also significant to note that dermal glyphosate absorption <u>does continue</u> beyond 24 hours. However, even at **36 hours post-application**, glyphosate concentrations **remained elevated** (mean 2.68 ng/ml) compared to the baseline (mean 0.94 ng/ml). Whereas in the inhalation exposure group at 24 hours post-application, urinary glyphosate concentrations had returned to baseline and only remained statistically significantly elevated for 12 hours post-application.

Routes of Exposure

The route of exposure controls how a chemical is absorbed into the body. The primary routes by which potential toxins become absorbed into a person's system are (a) ingestion, (b) inhalation and (c) dermal absorption.

Ingestion

Ingestion of herbicides may be intentional (as in suicides and poisonings) or unintentional through the consumption of residue-laden foods. In the current matter of assessing exposure in operator use, intentional ingestion is not considered since it will contribute negligibly to the overall exposure.

Inhalation

Since the vapor pressure of glyphosate is very low ($9.8x10^{-8}$ mm Hg or $1.31X10^{-2}$ mPa at 25˚C),[204] inhalation during mixing and preparation of an herbicide is typically not a significant contributor to exposure unless an aerosol is produced. Thus, inhalation during spray application of the herbicide can be a factor. Such exposure depends mainly on droplet size of the spray and the equipment used for spraying. Different nozzle types (often modified by farmers to increase discharge) will generate different volumetric droplet size distributions. Lesmes-Fabian, et al., found that for the standard discharge nozzle as used in their study, approximately 5% of the total volume of droplets was smaller than 100 µm.[205] In dry climates, droplets less than 100 µm are subject to evaporation and are respirable.

Respirable Dust and Atmospheric Glyphosate Exposure**

Sousa, et al., (2019)[206] conducted a study evaluating atmospheric pollution caused by use of glyphosate herbicide. The authors evaluated contamination by glyphosate in the atmosphere and association with total suspended particulate in urban and rural zones in Limoeiro do Norte, Brazil. They performed air sampling over a period of four months. Concentrations of the total suspended particle level (TSP) and glyphosate were estimated by gravimetric and liquid chromatography methods, respectively.

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[204] National Toxicology Program, U.S. Department of Health and Human Services.

[205] Lesmes-Fabian, C., Garcia-Santos, G., Leuenberger, F., Nuyttens, D., & Binder, C. R, "Dermal exposure assessment of pesticide use: The case of sprayers in potato farms in the Colombian highlands," 2012, Science of the Total Environment, 430, pp. 202-208.

[206] Sousa, M.G. de F., et al., "Evaluation of atmospheric contamination level for the use of herbicide glyphosate in the northeast region of Brazil," 2019, Environ Monit Assess, Vol. 191(10).

TSP levels found in urban and rural zones varied between 3.87 and 97.9 µg/m^3 and 10.8 and 137.4 µg/m^3, respectively. Concentrations of glyphosate in particulate matter in urban and rural zones varied between 0.009 and 2.576 µg/m^3 and 0.002 and 0.144 µg/m^3, respectively. The median concentration of glyphosate in the rural zone (where glyphosate is used) is 0.055 µg/m^3. The highest levels in the urban zone can be attributed to dispersion of pollutants through drift of wind. **Figure 8** illustrates the study findings.

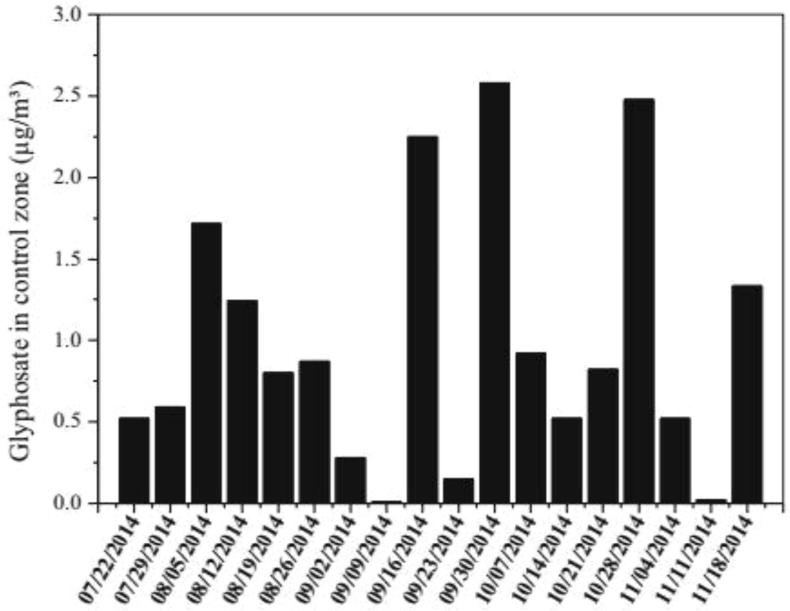

Figure 8: Profile of glyphosate (µg/m^3) over 4 months in Limoeiro do Norte, Brazil (2014)

It is highly noteworthy that both urban and rural glyphosate concentrations were found to be tens of thousands of times higher than those reported in literature of other countries; thus, revealing concerning levels of atmospheric glyphosate contamination.

In an unrelated but relevant study, Haberkon, et al., (2020)[207] analyzed glyphosate and aminomethylphosphonic acid (AMPA) respirable dust (RD) concentrations in Argentina shortly after herbicide applications. A positive relationship was determined between glyphosate in aggregates and glyphosate in RD ($p < 0.05$) indicating that aggregates with higher glyphosate concentration emitted a more glyphosate-enriched RD.

[207] Haberkon, N.B.R., et al., "Glyphosate and AMPA concentrations in the respirable dust emitted experimentally by soil aggregates shortly after herbicide application," 2020, Geoderma, Vol. 369, 114334.

The RD emitted by the finest aggregates showed the highest glyphosate concentrations. The higher glyphosate and AMPA concentration in RD suggest that soils with high contents of both compounds could emit RD with higher glyphosate and AMPA contents. Concentrations of glyphosate vary between 35 and 1,502 µg/kg and AMPA concentrations vary between 299 and 2,256 µg/kg in soils of Argentina. **Figure 9** from the published study reveals the study findings and respective concentration levels.

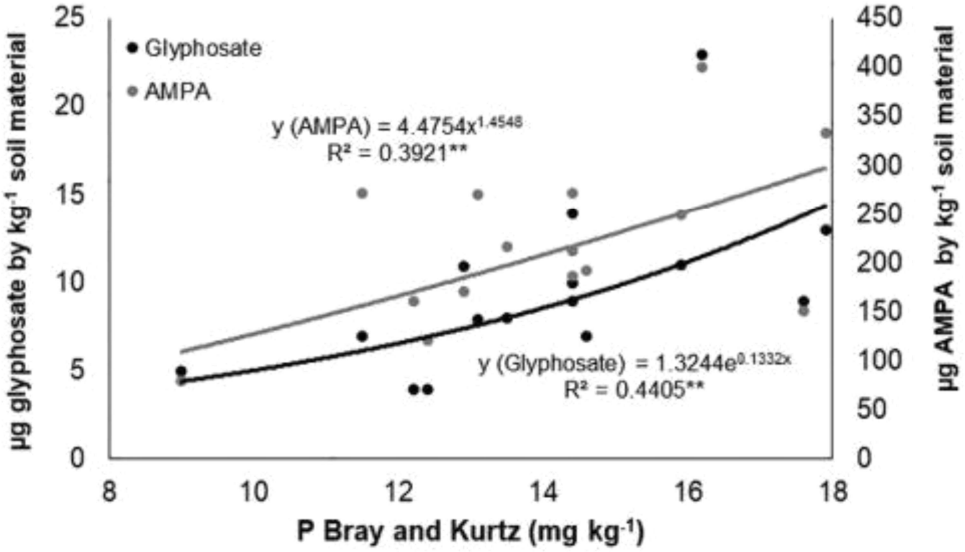

Figure 9: Glyphosate and AMPA content in aggregate fractions of field soil. **Significant p < 0.01

The study revealed that RD emitted by soils in which transgenic crops are produced has a potential risk of environmental contamination by transporting particulate matter containing high levels of glyphosate and AMPA.

Dermal Absorption

For occupational users such as applicators, home garden users and farmers, a key determinant of a person's exposure is how the herbicide is actually handled and/or applied.[208] Dermal exposure will occur throughout the mixing, loading and application of herbicides as well as through re-entry (i.e., handling stems, leaves or soil after herbicide treatment).

Studies have found that workers performing the common farm task of "thinning" are more exposed to pesticides than, for example, workers who are harvesting or pruning.[209,210] One study[211] found a higher level of pesticides in the house and vehicle dust of the thinning workers. Additionally, their children revealed higher urinary pesticide metabolite concentrations which showed evidence of a "take-home pesticide pathway."[212] The same study showed that workers in apple or pear crops had higher pesticide metabolite concentrations than those who worked in peach, cherry or grape crops.[213]

A 1995 Caltrans study[214] set out to verify that worker protection measures were effective in minimizing exposure to herbicides. The study evaluated exposure estimates in Caltrans VCP application employee activities (herbicide mixing, loading and application) by measuring dermal exposure for 18-worker days. The data was then compared to surrogate data produced by the Environmental Impact Report. This study revealed that higher, daily absorbed doses of glyphosate occurred from hand-wand application (1.4 mg/kg/day difference) versus a boom application using handgun despite that hand wand application resulted in significantly less handling of material compared to the boom application. The study staff observed that hand wand applicators were less careful about

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[208] Curwin, B.D. et al., "Urinary and hand wipe pesticide levels among farmers and non-farmers in Iowa," 2005, Journal of Exposure Analysis and Environmental Epidemiology, Vol. 15, pp. 500–508.

[209] de Cock, J. et al., "Determinants of exposure to captan in fruit growing," 1998, Am Ind Hyg Assoc J 59, 1998a, pp. 166–172 and 1998b, pp. 158-165.

[210] Simcox, N.J. et al., "Farmworker exposure to organophosphorus pesticide residues during apple thinning in central Washington State," 1999, Am Ind Hyg Assoc J 60, pp. 752–761.

[211] Coronado, GD, Thompson, B, Strong, L, Griffith, WC, and Islas, I., "Agricultural task and exposure to organophosphate pesticides among farm workers," 2004, Environ Health Perspect 112, pp.142–147.

[212] The take-home pesticide pathway is the pathway that children and spouses of agricultural workers are exposed through. (Hyland, C. and Ouahiba Laribi, Q., "Review of take-home pesticide exposure pathway in children living in agricultural areas," 2017, Environmental Research. Volume 156, pp. 559–570.)

[213] Coronado, GD, et al., "Organophosphate pesticide exposure and work in pome fruit: Evidence for the take-home pesticide pathway," 2006, Environ Health Perspect 114 (7), pp. 999-1006.

[214] Edmiston, S., et al., "Exposure of Herbicide Handlers in the Caltrans Vegetation Control Program 1993-1994," 1995, California EPA, California Department of Transportation

keeping the nozzle close to the ground and often raised the nozzle for difficult to reach areas which exposed the applicator to significant spray drift.

Mechanisms of Absorption

Farmers, forestry workers, home gardeners and landscapers are primarily exposed to herbicide chemicals through dermal contact during mixing, loading or application of the glyphosate formulation as well as through re-entry. Therefore, with respect to occupational exposure, the skin is the predominant route by which glyphosate enters the human body.

The Dermal Barrier

Human skin is a complex organ consisting essentially of two layers: a thin, outermost layer called the epidermis and a much thicker under-layer called the dermis. It is the outer layer of the epidermis, known as the stratum corneum (SC), that provides the primary protective barrier function of the skin. This barrier is largely responsible for resisting the entry of foreign agents into the human body.

The stratum corneum is primarily composed of non-living cells, or corneocytes, in a brick and mortar type system of lipid matrix. Corneocytes are terminally differentiated keratinocytes that have migrated from the epidermis to the skin's surface. The composition of the stratum corneum lipid matrix is dominated by three lipid classes: (1) cholesterol, (2) free fatty acids and (3) ceramides which are waxy lipid molecules. These lipids adopt a highly ordered, three dimensional structure of stacked, densely packed lipid layers[215] as shown in **Figure 10** and **Figure 11**.

[215] Van Smeden, J. and Bouwstra, J.A., "Stratum corneum lipids: Their role for the skin barrier function in healthy subjects and atopic dermatitis patients," 2016, Curr Prob. Dermatol 49, pp. 8-26.

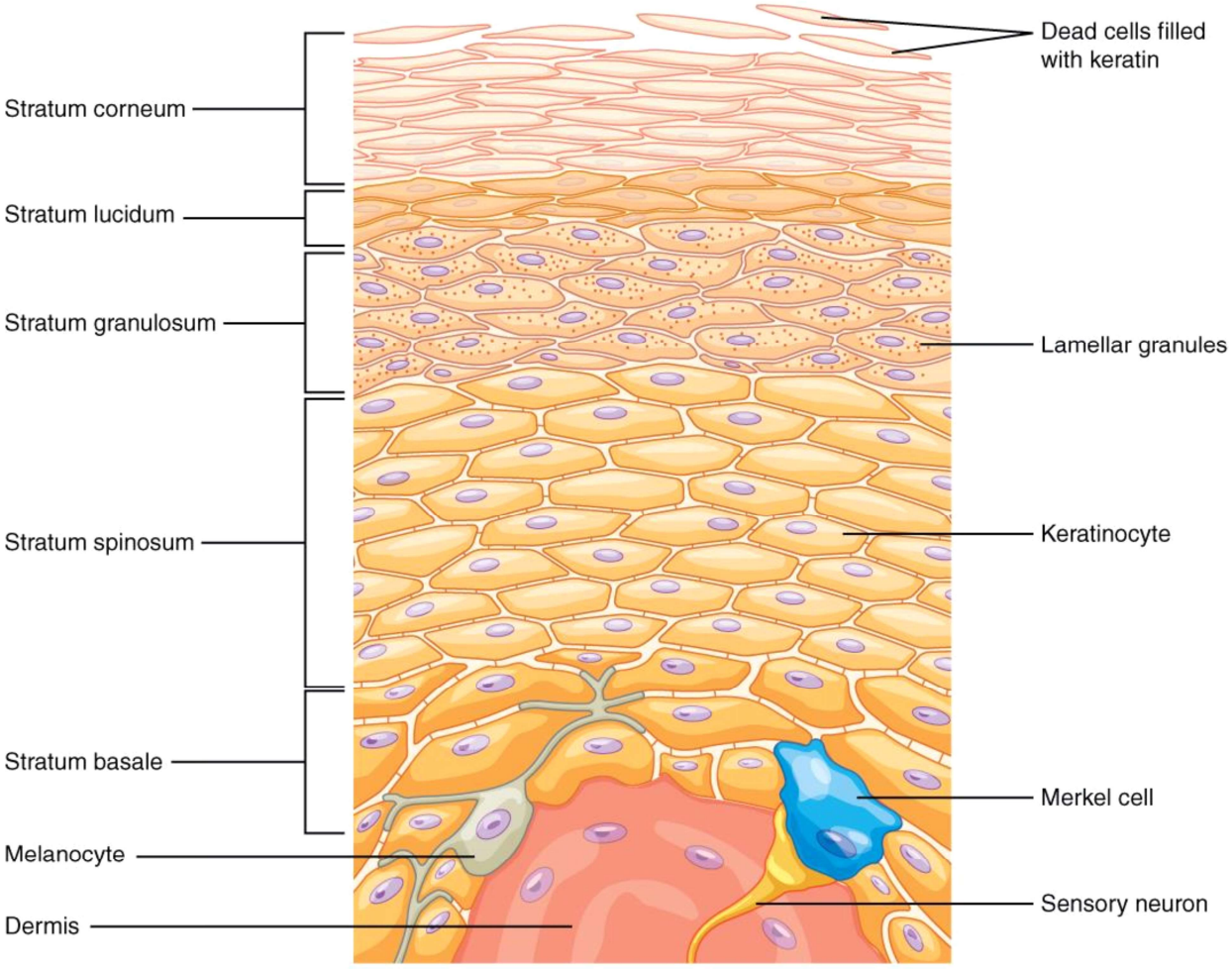

Figure 10: Epidermal Layers of Human Skin
Image courtesy of Wiki Journal of Medicine

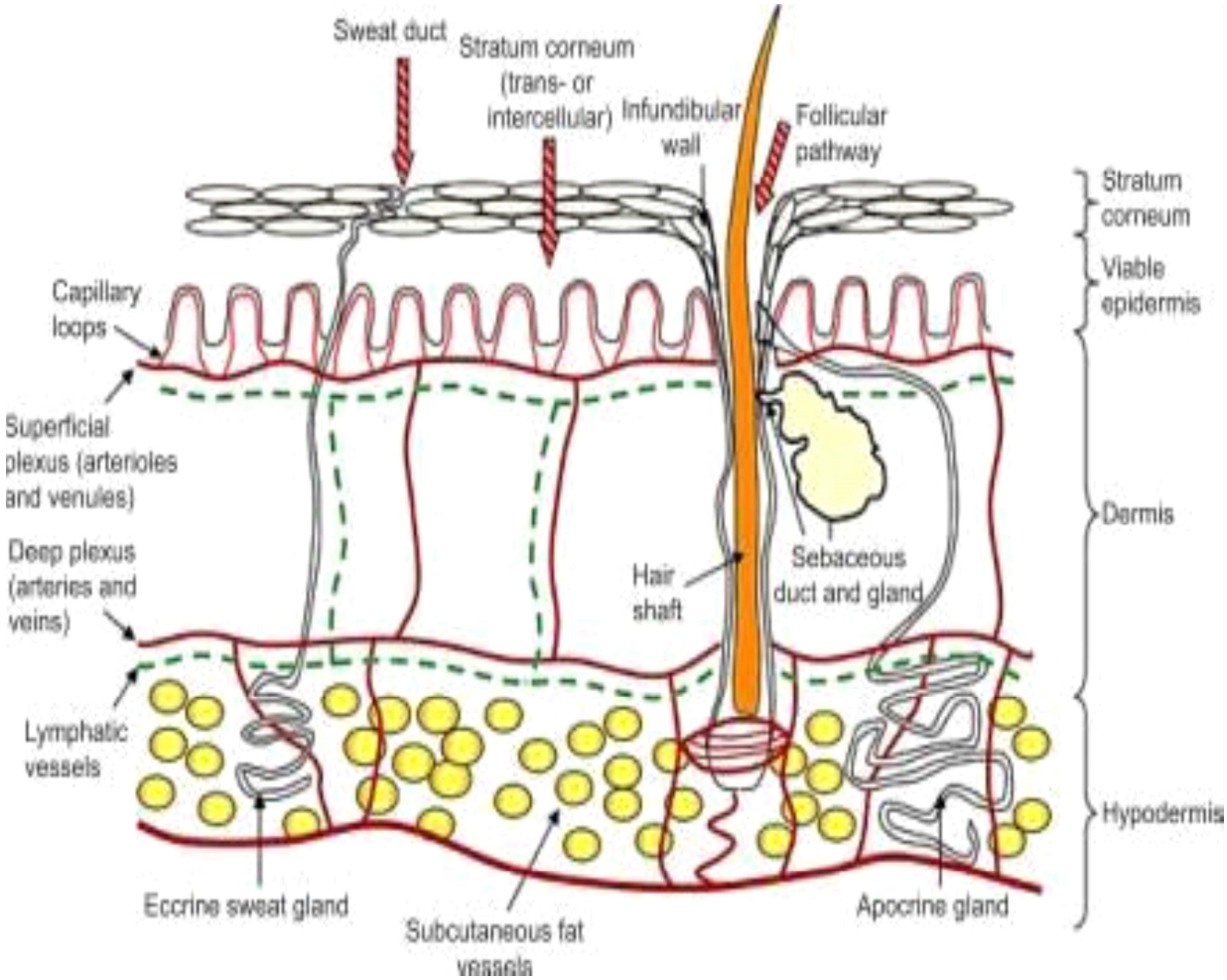

Figure 11: Layers of the epidermis, basal cell layer, stratum spinosum, stratum granulosum and the stratum corneum showing dermal penetration (Abd, 2016)[216]

[216] Abd, et al., "Skin models for testing of transdermal drugs," 2016, Clin Pharmacol, pp. 163–176.

Percutaneous Absorption of Glyphosate

A chemical can enter the stratum corneum directly through the corneocyte cells, through channels between the cells or through follicles, pores and glands. Due to its structure, the stratum corneum is highly lipophilic (lipid loving) and hydrophobic (tending to repel water). Thus, lipid-soluble chemicals are able to penetrate this layer into the circulatory system much more efficiently than water-soluble chemicals.

Since glyphosate is a small hydrophilic molecule, it travels easily through the channels and follicles; however, it cannot easily pass through lipid layers. The stratum corneum is, therefore, the rate-limiting barrier in the absorption of a hydrophilic agent such as glyphosate. The rate at which glyphosate passes through this outer layer determines the overall absorption rate of the chemical into the body.

Once glyphosate has been absorbed into the stratum corneum, it may pass through into the viable epidermis and then into the dermis where it is transported systemically by the dermal blood supply or lymphatics and circulated to other areas of the body. This passive diffusion process is governed by Fick's law which states that the rate of absorption or flux (J) of any substance across a barrier is proportional to its concentration difference across that barrier.

The stratum corneum is resistant to penetration of weak acids but is much less effective against organic acids and some inorganic chemicals. Organic and alkaline chemicals can soften the keratin cells in the skin and pass through this layer to the dermis where they are able to enter systemic circulation.

The thickness of the skin, as well as its lipophilicity, varies with location on the body. Areas of the body such as the forearms, which may be particularly hairy, are most easily penetrated by chemicals since they can enter the small ducts containing the hair shafts. Chemicals can also enter through cuts, punctures or scrapes of the skin since these are breaks in the protective layer. Due to the nature of their occupation, the skin of farmers (particularly their hands) typically has a higher percentage of fine cracks and breaks than that of the average person.

Percutaneous Absorption Models

The term "percutaneous" refers to any action involving penetration of the skin. Accurate determination of the rate at which agents penetrate the skin is critical for assessing the dose and potential risk from exposure. Dermal penetration is generally considered to occur by passive diffusion (Fick's law); however, in living organisms, biotransformation of a substance within the deeper viable regions of the skin (via metabolism) can also occur prior to systemic absorption.

The amount of a chemical that is absorbed through the skin is dependent on the properties of both the chemical and the skin. The most significant properties impacting the absorption of a chemical are its water and lipid solubility, molecular weight, degree of ionization and polarity.[217] The most important properties of the skin are the number (density) of follicles, the thickness of the stratum corneum and the sebum composition as well as the distance of capillaries to the surface of the skin.

Dermal penetration studies are conducted to measure the absorption or penetration of a substance through the skin barrier and into the skin and determine whether it has the potential to be absorbed into the systemic circulation. A wide range of experimental protocols exist for the determination of percutaneous absorption; the protocol used in any particular experiment will depend on the penetrant being studied.

Penetration studies may be conducted *in vivo* (in whole living animals) or *in vitro* (outside of a living organism). In assessing the risk of human exposure to glyphosate, the aim of a dermal absorption study is to measure the amount of glyphosate that passes into and through human skin and into systemic circulation.

Due to greater differences between rodents and humans versus primates and humans, *in vivo* human studies would provide the most accurate dermal penetration models. However, inasmuch as such studies would be both impractical and unethical, animals such as rats, mice, and monkeys are used for *in vivo* studies of the absorption of glyphosate.

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[217] Van Ravenzwaay, B. and Leibold, E., "A comparison between *in vitro* rat and human and *in vivo* rat skin absorption studies," 2004, Toxicol. *In Vitro*. Vol. 18(2), pp. 219-25.

Dermal Absorption *In Vivo* Measurement Methods

In vivo dermal absorption measurement methods include two methods: (1) the indirect method of surface disappearance and surface recovery whereby the dermal absorption is inferred and (2) direct methods of determining dermal absorption which includes measuring glyphosate in the blood, excreta (urine or feces) or stratum corneum or by estimating through biological or pharmacological responses.[218]

Zendzian, 2000,[219] published a method for measuring glyphosate in excreta and in carcasses as well as the quantity remaining in the skin after washing. The Zendzian study states that the U.S. EPA's Office of Pesticide Programs (OPP) has developed a standard protocol for evaluating the dermal penetration of pesticides in the rat. This protocol was formalized in 1994 as a guideline for dermal absorption studies of pesticides.

As of the year 2000, in excess of 263 studies on the dermal absorption of over 160 pesticide chemicals had been submitted to OPP as part of the pesticide registration and risk assessment processes. From this standard protocol, it is possible to describe quantitatively (via dose and time) the entrance of a chemical into and penetration through the mammalian epidermis into the systemic circulation as well as the chemical's concentration in blood, the body and its excretion in urine and feces.

Dermal Absorption *In Vitro* Measurement Methods

Since *in vivo* studies are complex and expensive, *in vitro* methods are more widely used as a screening method for dermal penetration estimates. *In vitro* experiments involve the use of a diffusion cell wherein two chambers, donor and receptor, are separated by a membrane (human or animal skin). There are many variations, but all diffusion cells involve the penetrant passively diffusing from the donor chamber into the receptor chamber where it can be measured.

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[218] U.S. EPA, "Dermal exposure assessment: A summary of EPA approaches," September 2007. United States Environmental Protection Agency, National Center for Environmental Assessment Office of Research and Development, EPA/600/R-07/040F

[219] Zendzian, R.P., "Dermal absorption of pesticides in the rat," 2000, AIHAJ, Vol. 61(4), pp. 473-83.

In 2007, the U.S. EPA published "Dermal Exposure Assessment: A Summary of EPA Approaches" which provides a dermal exposure assessment methodology for treated surfaces.[220] The U.S. EPA and other regulatory agencies accept a wide diversity of *in vitro* protocols, but they caution comparing these studies due to differences in study conditions. These include cell type (*i.e.,* static or flow through), the membrane selected, composition of the receptor fluid and the dosing method (infinite or finite).

Other Measurement Models and Methods

In a static diffusion cell, also known as a Franz cell,[221] the penetrant diffuses from the donor chamber through the membrane into a "static" receptor chamber of a fixed volume which is continually stirred. In a flow through cell or Bronaugh[222] cell, *in vivo* conditions are simulated by using a constantly flowing receptor fluid that mimics *in vivo* blood flow beneath the skin membrane. The skin membrane is bathed below by a flowing solution maintained at 37 degrees C.

When studying the absorption of glyphosate, the membrane separating the chambers is typically human (from cadavers), rat or monkey skin and may be full thickness or dermatomed (sliced). Dermatomed skin, wherein only the epidermis is used after it has been separated from the dermis, is commonly used because full-thickness skin can be cumbersome in the diffusion apparatus. Since glyphosate is hydrophilic, the main barrier to its diffusion across the skin resides in the stratum corneum and, therefore, the absence of the dermal tissue is generally not of concern.[223] Ideally, when fresh skin is used, the receptor fluid should allow skin metabolic activity.

Franz did caution that, for compounds that have a slow absorption rate, *in vivo* methods may underestimate total absorption value significantly. Thus, absorption rates of the

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[220] U.S. EPA, "Dermal exposure assessment: A summary of EPA approaches," September 2007. United States Environmental Protection Agency, National Center for Environmental Assessment Office of Research and Development, EPA/600/R-07/040F

[221] Franz TJ., "Percutaneous absorption. On the relevance of *in vitro* data," 1975, J Invest Dermatol. Vol. 64, pp. 190–5.

[222] Bronaugh, R., H. Hood, M. Kraeling, and J. Yourick, "Determination of percutaneous absorption by *In Vitro* techniques," 1999, pp. 229-233 in Percutaneous Absorption, 3rd ed., R.L. Bronaugh and H.I. Maibach, eds. New York: Marcel Dekker, Inc.

[223] Williams, A.., "Transdermal and dermal drug delivery: From theory to clinical practice," 2003, London, Pharmaceutical Press.

compound may considerably affect the total absorption value between *in vitro* and *in vivo* methods.[224]

Dosing Techniques and Measurement Considerations

The loading (or dosing) of the donor chamber in all diffusion cells is accomplished in one of two ways: (1) infinite dosing or (2) finite dosing.

In the infinite dosing, or flux, technique, a high concentration of glyphosate is installed into the donor chamber (so its concentration does not decrease) while the concentration is measured in the receptor chamber over time until steady state is reached. This allows for the calculation of a permeability coefficient. The finite dose technique allows the herbicide to be tested under conditions similar to those found *in vivo*. The donor chamber is loaded with a known amount of herbicide which is depleted due to penetration during the course of the experiment. The concentration of the herbicide in the receptor fluid is measured to determine the percent of the original dose that penetrated the skin per unit area of skin over a period of time.

Loading conditions can greatly impact calculation of percent absorption. As the applied dose becomes greater than the absorbable amount, the excess does not contribute to absorption but it does diminish the observed percent of dose that is absorbed.[225] Therefore, when comparing *in vitro* results of percent absorption, all the dosing conditions should be maintained as finite dose applications rather than flux.[226]

Rat skin is generally (but not always) more permeable than human skin. In a review of 79 studies which measured absorption of 110 chemicals, four chemicals were found that are less permeable through rat skin than human skin.[227] Van Ravenzwaay also found that in comparing human *in vitro* skin with *in vivo* rat skin, the penetration of 3 of 12 chemicals

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[224] Franz TJ., "Percutaneous absorption. On the relevance of *in vitro* data," 1975, J Invest Dermatol. Vol. 64, pp. 190–5

[225] Frasch, H.F. et al., "Analysis of finite dose dermal absorption data: Implications for dermal exposure assessment," 2014, J Expo Sci Environ Epidemiol, 24(1), pp. 65–73.

[226] "Guidance Notes on Dermal Absorption," OECD Environment, Health and Safety Publications, Series on Testing and Assessment No. 156. ENV/JM/MONO(2011)36.

[227] Jung, E, and Maibach, H., "Animal models for percutaneous absorption," 2014, in Shah, V., Maibach, H., and Jenner, J. eds. Topical Drug Bioavailability, Bioequivalence, and Penetration, 2nd ed. New York: Springer, pp. 21-40.

was greater through human skin than through rat skin. This held true at 4, 8 and 10 hours after dosing.[228]

A recent study has also questioned the reliability of converting percutaneous absorption data from rats to humans due to the differences in species as the absorption of hazardous substances was studied.[229]

In Vitro Dermal Absorption of Herbicides through Rat versus Human Skin

The use of rat skin in percutaneous absorption models is premised on the theory that rat skin is generally more permeable than human skin; however, there have been some cases which have reported that rat skin is less permeable.[230]

Monsanto attempted to demonstrate (and failed) that the dermal penetration of Propachlor® (2-chloro-N-isopropyl-N-phenylacetamide) through human skin was lower than in rat skin. Instead, the study revealed:

- Concentrate formulation: The percent penetration with human skin **is equal to** the percent penetration with rat skin.
- Spray dilution: The percent penetration with human skin **is greater than** the percent dermal penetration with rat skin ($p<0.05$).
- Microautoradiographies clearly revealed **stores** of Propachlor in the epidermis of human skin.[231]

"Triple Pack" Methodology

The term "Triple Pack" refers to the use of three types of dermal absorption data from: 1) *in vivo* rat; 2) *in vitro* rat and 3) *in vitro* human dermal absorption studies.[232] This approach is used to refine the estimation of dermal absorption by correcting for differences between *in vitro* and *in vivo* absorption rates in rats as well as for species differences between rats

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[228] Van Ravenzwaay, B. and Leibold, E., "A comparison between *in vitro* rat and human and *in vivo* rat skin absorption studies," 2004, Toxicol *In Vitro*., Vol. 18(2), pp. 219-25.

[229] Korinth G, et al., "Discrepancies between different rat models for the assessment of percutaneous penetration of hazardous substances," 2007a, Archives of Toxicology 81, pp. 833-840.

[230] Hotchkiss, SA, et al., "Percutaneous absorption of 4,4'-methylene-bis (2-chloroaniline) and 4,4'-methylenedianiline through rate and human skin *in vitro*," March 1993, Toxicology *In Vitro*, Volume 7(2), pp. 141-148.

[231] Monsanto email (Tab 21) from [redacted] on 3/29/2002 to [redacted] et al.

[232] U.S. EPA OPP Memorandum June 2, 2010. "Review of Triple Pack dermal absorption studies for Maxim Quattro."

and humans.[233] The "Triple Pack" approach is based on the premise that the absorption difference between humans and rats will show in the same proportion in both *in vitro* and *in vivo* test (which may not be true). It should also be noted that the "Triple Pack" approach should be used to estimate a dermal absorption value only when the three studies are conducted under the same experimental conditions.[234]

Monsanto has recently (2010 – 2017) contracted with Dermal Technology Laboratories (DTL), Ltd. However, only *in vitro* **human cadaver skin** has been used (although potentially removed from living subjects through surgical reduction procedures). Most importantly, the DTL studies **fail to include** the "Triple Pack" methodology.

It was found by Wester, et al.,[235] that the common practices of freezing skin for storage or heat treatment to separate epidermis from dermis, can destroy skin viability.[236] The authors found that storing dermatomed skin human cadaver skin in a sustaining media[237] can maintain energy viability for up to eight days. They recommend not using skin that has been heat separated or frozen in absorption studies where skin viability and metabolism might be contributing factors to the study.

More accurate measurement models generally include animal or primate *in vivo* measurements since *in vitro* human cadaver skin does not have an intact physiologic and metabolic system present to accommodate active blood capillary transport gradients or metabolism as do the *in vivo* models. This is especially true when skin is first heated to 60°C (140°F), dermatomed and then frozen at -20°C as has been done by DTL. Studies have shown there are species differences in the absorption of different chemicals; measurements in rats, rabbits or pigs may or may not reflect human absorption.[238] A more accurate model includes dermal absorption across primate (monkey) skin. Often,

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[233] Id.

[234] "Guidance notes on dermal absorption," OECD Environment, Health and Safety Publications, Series on Testing and Assessment No. 156. ENV/JM/MONO(2011) 36.

[235] Ronald C. Wester, Julie Christoffel, Tracy Hartway, Nicholas Poblete, and Howard I. Maibach, James Forsell, "Human Cadaver Skin Viability for In Vitro Percutaneous Absorption: Storage and Detrimental Effects of Heat-Separation and Freezing," Percutaneous Absorption, Drugs-Cosmetics-Mechanisms-Methodology, 4th Edition, Vol. 155, pp. 311-316.

[236] As measured by lactate production from glucose.

[237] Eagles minimum essential media with Earles balanced salt solution

[238] Rozman, KK and Klaassen CD., "Absorption, distribution and excretion of toxicants," in Cassarett & Doull's Toxicology, The Basic Science of Poisons. 5th edition. 1996. McGraw-Hill.

although not always, *in vivo* monkey skin most accurately resembles percutaneous absorption across human skin.

Dermal Absorption Correspondence Between Monsanto and DTL Laboratory

DTL's Managing Director, David Fox, was head of the *in vitro* percutaneous absorption group at Syngenta Central Toxicology Laboratory.[239] DTL was formed by former Syngenta employees in 2007. Email[240] from Simon Hill at Syngenta to David Saltmiras at Monsanto on January 20, 2009, reveals a discussion concerning dermal absorption as follows:

> "DTL uses different methods to prepare the skin samples." … "I believe that an *in vitro* dermal absorption study conducted on human epidermis with the concentrate formulation and at least one dilution (Syngenta would normally do 2) would be adequate to meet the EU criteria. With these studies, the amount of dermal absorption is dependent upon the level of surfactants in the formulation. I believe it is in everyone's best interested [sic] ***to get as lower a dermal absorption value as possible for the representative use***…"

The message then goes on to say:

> "…so, I have a couple of suggestions regarding dermal absorption The TWG discussed the fact that Monsanto had a biomonitoring study that the Spanish dismissed because of a non-human primate study that showed higher excretion in the feces than in the urine following a dermal exposure. I suggest that the TWG use a metabolism/dermal absorption consultant by the name of Brian Jones who could critically review the non-human primate dermal study and the likely metabolism (or lack of) of glyphosate following dermal exposure. Hopefully, he could **put a position together on the non-relevance of the findings** in the old non-human primate study. In addition, perhaps a package of dermal absorption studies (rat *in vivo* and human and rat *in vitro*) on the representative formulation may provide more detailed results and the *in vivo* study could be used to show that glyphosate is not metabolized and is mainly excreted in the urine (and the studies could also be used in the U.S. in the future)."

In fact, DTL did use *"a different skin preparation method,"* as described below.

DTL Laboratory Human Epidermis Preparation Methods

It is generally accepted and required laboratory practice to report the procedures used to prepare the epidermis for use in dermal absorption studies. A group of laboratory reports

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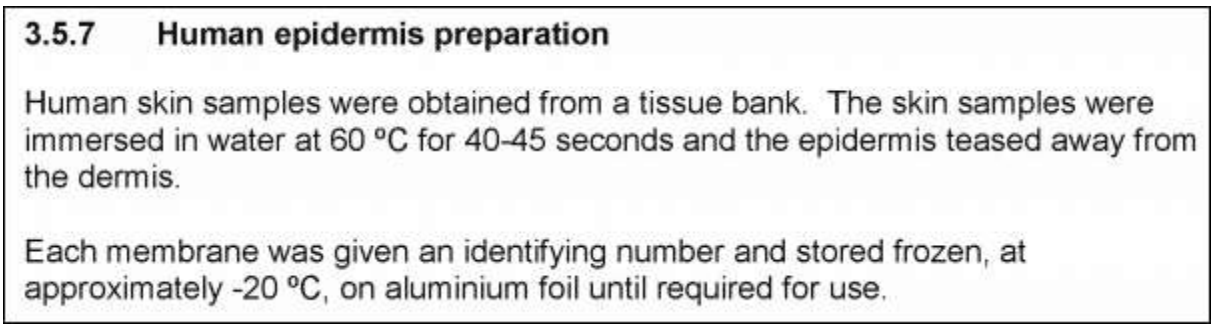
[239] "A Wealth of Expertise," DTL Laboratory, http://www.dermaltechnology.com/about/

[240] Email from Simon Hill, Syngenta Ltd., January 20, 2009, CC: [redacted] Monsanto

on various glyphosate formulations (*in vitro* absorption through human dermatomed skin) were issued to Monsanto by Dermal Technology Laboratory, Ltd., from 2010 – 2017.

Figure 12 describes the epidermis preparation procedure as stated in each *"Materials and Methods"* section in the four laboratory reports dated 2010:



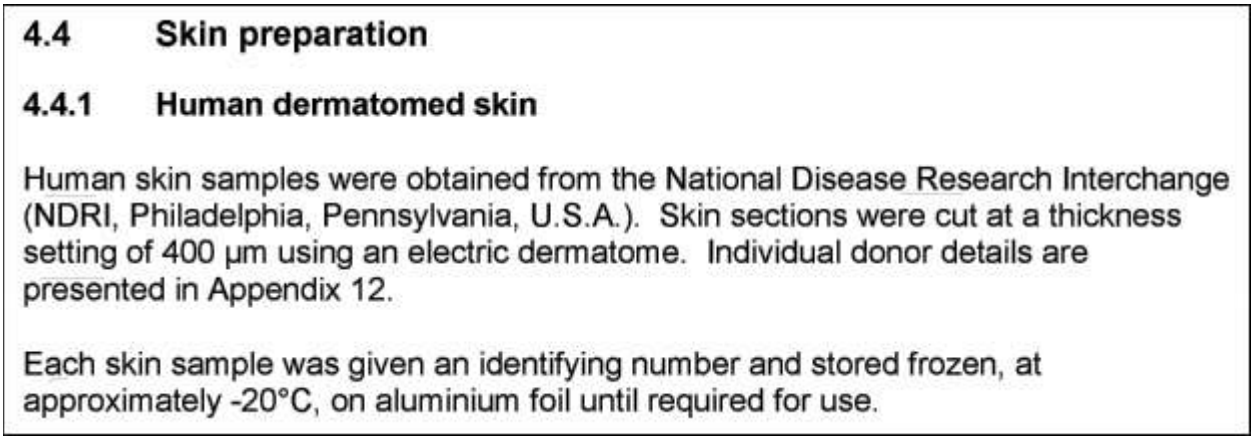
3.5.7 Human epidermis preparation

Human skin samples were obtained from a tissue bank. The skin samples were immersed in water at 60 ºC for 40-45 seconds and the epidermis teased away from the dermis.

Each membrane was given an identifying number and stored frozen, at approximately -20 ºC, on aluminium foil until required for use.

Figure 12: DTL Laboratory Epidermis Preparation Procedure (2010 Reports Only)

However, in the four subsequent reports (two dated 2015 and two dated 2017), this information was removed and a new (incomplete) preparation method description was included under "Experimental Procedures" as described in **Figure 13**:



4.4 Skin preparation

4.4.1 Human dermatomed skin

Human skin samples were obtained from the National Disease Research Interchange (NDRI, Philadelphia, Pennsylvania, U.S.A.). Skin sections were cut at a thickness setting of 400 µm using an electric dermatome. Individual donor details are presented in Appendix 12.

Each skin sample was given an identifying number and stored frozen, at approximately -20°C, on aluminium foil until required for use.

Figure 13: DTL Laboratory Epidermis Preparation Procedure (Post-2010 Reports Only)

Following 2010, no further mention was made in the reports of immersing ("cooking") the skin in water at 140° F (60 degrees C) for 40-45 seconds followed by freezing the skin at -20ºC prior to the subsequent dermal absorption analyses.

Numerous studies have been published using skin from different animal models. However, the knowledge that there is a significant difference in absorption when it comes to different animal species and humans has led to the necessity of a thorough

interpretation when adapting data from animal studies that are to be used in relation to humans. Interpretation of the data to refine dermal absorption values can vary between regulatory authorities.[241,242]

Dermal Absorption and Pharmacokinetic Studies of Glyphosate

Models Used to Measure Glyphosate Dermal Absorption

There are four primary models which have been used to measure glyphosate dermal absorption: (1) the Maibach studies of 1983, (2) the Wester et al., studies of 1991, (3) Franz (1983) and (4) TNO (2002). All of these studies were funded by Monsanto. This section reviews these studies and assesses the findings in light of present-day objective science.

Maibach Study (1983)

Full Title: Maibach, H.I. (1983) "(a) Elimination of ^{14}C-glyphosate in Rhesus monkeys following a single parenteral dose, (b) Percutaneous absorption of 14C-glyphosate in Roundup formulation in Rhesus monkeys following a single topical dose." Unpublished report No. MA-81-349, dated 1 April 1983, from University of California, School of Medicine; San Francisco, California, USA. Submitted to WHO by Monsanto Int. Services SA, Brussels, Belgium.

This Monsanto-funded study included human *in vitro* testing as well as an *in vivo* primate (monkey) testing. The test material was a Roundup formulation supplied by Monsanto; the formulation used was the mono isopropylamine salt of glyphosate. No surfactants or other adjuvants were listed as ingredients.

- Part (a): ^{14}C-Glyphosate (MON 0139; isopropylamine salt) was administered to four Rhesus monkeys through intramuscular (IM) injection. Maibach found that, on average, 89.9% of the injected dose was excreted in the urine. He did not, however, measure the amount of glyphosate eliminated in the feces. Maibach reported two distinct phases of urinary excretion: (1) 0-24 hours $t_{1/2}$ = 6.9 hrs. and (2) 1-7 days $t_{1/2}$ = 35.1 hrs., concluding that "*systemic doses of glyphosate in MON 039 are rapidly eliminated in monkeys, predominantly via the urine*."

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[241] "Guidance notes on dermal absorption," OECD Environment, Health and Safety Publications, Series on Testing and Assessment No. 156. ENV/JM/MONO(2011)36.

[242] U.S. EPA OPP Memorandum June 2, 2010. "Review of Triple Pack dermal absorption studies for Maxim Quattro."

- Part (b): ^{14}C-Glyphosate (MON 0139; isopropylamine salt) was dermally applied to Rhesus monkeys at a concentration of 1.13 mg/cm^2. The IM data from Part (a) was used to quantify the dermal penetration obtained in this part of the experiment.

There are problems with the findings of this study as explained below.

Since the majority of ^{14}C-Glyphosate administered by IM injection was excreted rapidly through the urine, Maibach erroneously assumed that 89.9% of the dermal dose would be eliminated in the urine as well. He used this correction factor for incomplete urinary excretion (89.9%) to determine that 1.8% of the applied dermal dose penetrated the skin. This conclusion was errant for several reasons:

1) Two different routes of exposure (IM versus dermal);
2) Two different paths of excretion (urinary and fecal);
3) Failure to measure the ^{14}C-Glyphosate excreted in the feces.

Additionally, a further error was made by assuming the unrecovered glyphosate was permanently bound in the skin. The skin-washing procedure removed 14.2% (standard deviation of 3.5%) of the applied ^{14}C-label on the glyphosate. Therefore, only 16% (14.2 + 1.8) of the dermally-applied glyphosate was recovered. The total percent recovery was low (*i.e.,* 16.0%). Although a definitive explanation cannot be offered for the low recovery, previous experience suggests that much of the test material may in some way bind to or in the skin and cannot be removed by washing. This bound material is not apparently available for systemic absorption."[243]

The key point is that this explanation is inconsistent with generally-accepted guidelines. For example, OECD guidelines[244] cite that an adequate mean recovery is in the range of 100 ± 10% (OECD, 2004). If the test material did indeed bind to or in the skin, then it could have been available for absorption and, according to guidelines given by OECD, would have to be included in the amount absorbed.[245]

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[243] Maibach, H.I., "(a) Elimination of 14C-glyphosate in Rhesus monkeys following a single parenteral dose, (b) Percutaneous absorption of 14C-glyphosate in Roundup formulation in Rhesus monkeys following a single topical dose," 1983, Unpublished report No. MA-81-349, from University of California, School of Medicine, San Francisco, California, USA. Submitted to WHO by Monsanto Int. Services SA, Brussels, Belgium.

[244] Guidelines require that at least 90% of the dose be accounted for compared to just 16% in the Maibach study.

[245] OECD/OCDE 427, "Guidelines for the testing of chemicals. Skin absorption *in vivo* Method," Adopted: 13 April 2004.

In 1985, the U.S. EPA classified the Maibach, 1983, study as unacceptable since the majority of the dose could not be accounted for. Currently, most authorized agencies calculate by "*absorbed amount + amount remaining in the treated area tissue + (when necessary) amount remaining in the skin tissue after a washing process*" when calculating the absorption amount.[246]

In communications regarding the Maibach study, Richard Dirks, Ph.D., Senior Product Toxicologist at Monsanto, wrote (April 11, 1983):

> *"The total percent recovery (percent label removed by washing plus total percent label contained in urine) was low, i.e., 16.0%. A definitive explanation for the low recovery is not provided in the report, but the author does state that previous experience would suggest that much of the test material may in some way bind to or in the skin and cannot be removed by washing. In support of this, it has been reported (Vickers, 1963) that a "chemical reservoir" is formed in the skin after drug application which is eventually shed without penetration. Thus, it is concluded that the bound material is not apparently available for systemic absorption."* [247]

It is critical to note that the OECD guidelines state that the amount of substance not found in the donor chamber must be considered absorbed and, therefore, potentially available in the systemic circulation. This also accounts for the amount of substance deposited in the skin.[248]

Subsequent experiments have demonstrated that absorption of chemicals temporarily deposited in the skin can continue for up to 24 hours or more after exposure has ended. Thus, temporary skin deposition will potentially underestimate the true absorption if assessed in blood or urine immediately following exposure (within 24 hours).[249]

Wester, et al., Study (1991)

Full Title: Wester, R. et al., "Glyphosate skin binding, absorption, residual tissue distribution and skin decontamination," 1991, Fundamental and Applied Toxicology 16, pp. 725-732.

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[246] Jaehwan, S., "Comparison of international guidelines of dermal absorption tests used in Pesticides Exposure Assessment for Operators," 2014, Toxicol Res 4, pp. 251-260.

[247] MONGLY01330783

[248] OECD, "Guidance document for the conduct of skin absorption studies," 2004a, Paris. 28, pp.1-31.

[249] "Dermal absorption of pesticides – evaluation of variability and prevention," 2009, Danish Environmental Protection Agency. Pesticides Research No. 124, 13.1.

This Monsanto-funded study included human *in vitro* testing as well as *in vivo* primate (monkey) testing. The test material was a Roundup formulation supplied by Monsanto; it is not stated what glyphosate salt was used in the formulation. The exact formulation was not disclosed, but no surfactants or other adjuvants were listed as ingredients.

In vitro human skin absorption: A finite dose technique was used with human plasma as the receptor fluid in a flow-through diffusion cell. Dosing concentrations ranged from 2.6 µg/cm^2 to 154.0 µg/cm^2 with exposure times of 30 minutes, 4 hours, 8 hours and 16 hours. The greatest absorption (2.2 ± 0.5 %) occurred at the lowest glyphosate dose concentration (2.6 µg/cm^2) after 8 hours of exposure. This was more than twice that which was absorbed at any of the other dose concentrations after 8 hours.

The data in this study is highly variable, *i.e.,* it shows no discernable pattern with respect to the dose and time of exposure other than that the highest percentage of absorption occurred at the lowest dermal dose. The standard deviation of the mean was greater than the mean for 12 of the 20 means reported. No overall accountability (mass balance) was provided for this part of the study; no data was provided with respect to how much glyphosate was lost. Thus, it was not possible to compare the percentage lost to that of the *in vivo* dermal study.

In vivo rhesus monkeys' IV doses: Three Rhesus monkeys were intravenously dosed with 93 µg glyphosate and three were dosed with 9 µg glyphosate. The study found that in the six monkeys, 95% - 99% of the IV administered dose was recovered in the urine. Overall accountability was greater than 96% of the administered doses. Wester, et al., used these results to make the assumption that all dermally-absorbed glyphosate would similarly be excreted in the urine. This assumption is invalid according to their data reported in the next part of the study (see below).

In vivo rhesus monkeys' dermal dosing**:** Eight monkeys were dermally dosed with one of two doses as summarized in **Table 15**.

Table 15

Disposition of Glyphosate Following Topical Administration to Rhesus Monkeys[250]

Disposition Site	Percentage of applied dose*	
	Dose C = 5400 µg/20 cm^2	Dose D = 500 µg/20 cm^2
Urine	2.2 ± 1.5	0.8 ± 0.6
Feces	0.7 ± 0.5	3.6 ± 1.6
Urine + Feces	**2.9 ± 2.0**	**4.4 ± 2.2**
Surface Washes	73.5 ± 6.0	77.1 ± 9.2
Contaminated Solids	0.05 ± 0.1	0.3 ± 0.1
Total	**76.5 ± 6.7**	**81.8 ± 6.9**

Topical administration in four Rhesus monkeys per dose: *Each value is the mean ± SD for 4 monkeys."

The above data reveals several critical findings:

1) The low topical dose was excreted primarily in the feces. In the monkeys administered Dose D, 3.6 % of the dermally-applied dose was recovered in the feces whereas only 0.8 % was recovered in the urine (**total dermal absorption of 4.4%).** From this data, it is apparent that **urine recovery does not accurately represent the amount of glyphosate that was dermally absorbed**. In this case, 4.5 times more glyphosate was found in the feces than in the urine.

2) This study finding is deeply troubling since epidemiology studies rely on urine concentrations to quantify the systemic dose of glyphosate exposure through dermal absorption. The lower dose (Dose D) at 500 µg/20 cm^2 corresponds to real world exposures in farmers and applicators. Thus, the exposure studies prepared by Monsanto that have relied on urinary excretion are in error by a factor of 4.5 times the current calculated values. From the data in this study, the total systemic dose from dermal exposure can be calculated:

$$GLY_{systemic} = GLY_{urine} + GLY_{feces}$$
$$= GLY_{urine} + 4.5 \times GLY_{urine}$$
$$GLY_{systemic} = 5.5 \times GLY_{urine}$$

[250] Wester, R. et al., "Glyphosate skin binding, absorption, residual tissue distribution and skin decontamination, 1991, Fundamental and Applied Toxicology 16, pp. 725-732.

The actual systemic dose in the human epidemiological exposure studies could have been accurately quantified by including the relative amount of glyphosate that would have been excreted in the feces but which was not measured.

3) The dose of 5,400 µg/20 cm^2 is too large to accurately represent the dose/absorption relationship. As previously explained, dosing conditions can have enormous effects on percent absorption. The excessive dosing in this case is approaching infinite dosing and the excess does not contribute to absorption, but it does diminish the calculated percent of dose absorbed.[251] U.S. EPA guidelines for dermal testing recommend a maximum practical dose on the order of 1 mg/cm^2; larger doses can exceed saturation of the absorption process.[252] The resulting error herein is an artificially reduced percent absorption; this high saturation dose resulting in 2.9% absorption is not relevant when looking at percent absorption.

4) The effect of glyphosate on skin has been shown to depend on the relative concentration of glyphosate. Dermal cells exposed to low levels of glyphosate have been shown to induce a stiffening of the cytoskeleton (the cell's internal structural support) while higher levels of glyphosate cause gross changes in cell shape.[253] As realistic exposure levels were not used, the findings are automatically suspect.

5) Only 81.8 % of the applied "Dose D" was recovered. The authors claimed that the remaining 18.2 % was "lost" since it was not detected. If any of the missing 18.2% remained in the monkey in tissue or fluid that was not tested, the amount absorbed would have been underestimated. The lost material is beyond the acceptable limit according to OECD guidelines of mass balance. If all of the missing 18.2 % is assumed to have remained in the monkey and is included the amount absorbed, the total % of applied dose absorbed becomes 22.6%. Either way, a casual and unverifiable "claim" that 18.2% of the dose was "lost" can scarcely be regarded as objective and should be added to the amount absorbed (4.4%) to provide an upper limit value of 22.6%.

6) The impact of surfactants on absorption is still not considered in this study.

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[251] Frasch, H.F. et al., "Analysis of finite dose dermal absorption data: Implications for dermal exposure assessment," 2014, J Expo Sci Environ Epidemiol, Vol. 24(1), pp. 65–73.

[252] U.S. EPA OPPTS 870.7600, "Health effects test guidelines dermal penetration," August 1998, pg. 4.

[253] Heu, C. et al., "Glyphosate-induced stiffening of HaCaT keratinocytes, a peak force tapping study on living cells," 2012, Journal of Structural Biology, 178, pp. 1-7.

From Wester, et al., it is reasonable to conclude that dermal absorption at "Dose D" reasonably estimates a dermal absorption dose ranging from **4.4% to 22.6%**. More importantly, the epidemiological exposure studies underestimate the systemic dose from dermal absorption by a factor of 4.5 due to the failure to consider hepato/fecal elimination at the lower dose levels.

Concern of Cross-Contamination in the Wester, et al., Study (1991)

The rhesus monkeys were placed in metabolic chairs for the dosage period (12 hours) of the study, then housed individually in metabolic cages. A belly plate and apron were positioned on the metabolism chair under the skin-dosing site. A pan collected urine, feces and other solids such as residual food and hair. Surface washes collected the residual dose left on the skin.

Only 75-80% of the dermally applied dose was recovered in all the collections. Wester noted that the missing 20-25% dose was "lost" during the procedure, and he considered this not to be unusual as similar losses had occurred in previous studies. He attributed the loss to exfoliation of skin which "*will scatter microscopic tissue and bound chemical to the atmosphere, making total accountability impossible to achieve*."

Wester did not mention any other mechanisms of loss, such as monkeys touching the dosing sites, which would have easily explained the unacceptable 20-25% loss of the dose amount. Therefore, it is reasonable to conclude that such losses did not occur.

Metabolic chairs come in various configurations as shown in the images below as different types of research will require different restraining needs. These "chairs" allow for the isolation of body parts with the use of belly plates, restraints, etc. (See **Figure 14** and **Figure 15**).

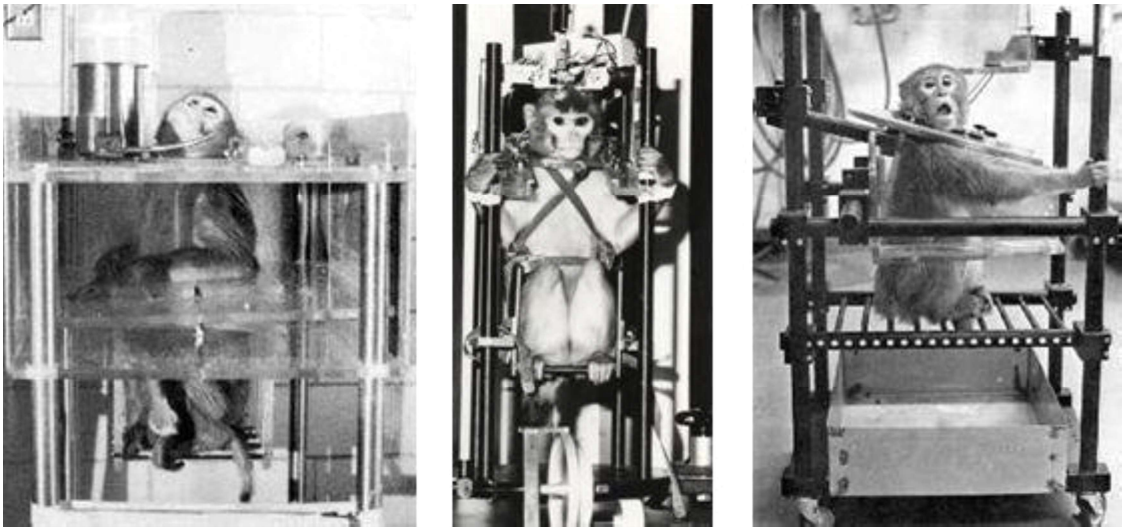

Figure 14: Metabolic chairs for primates[254]

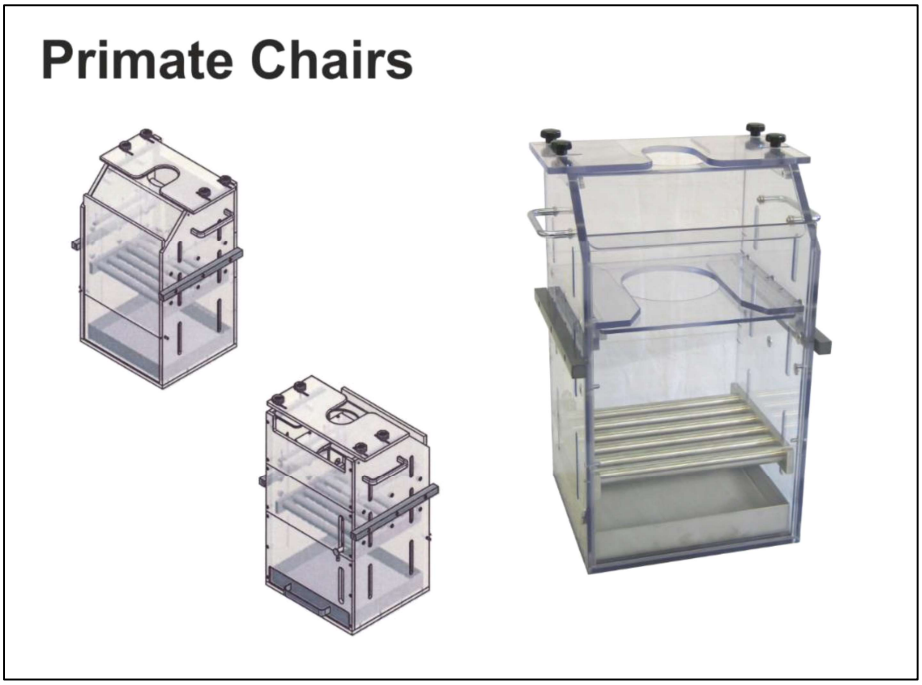

Figure 15: Primate chairs used in study testing

[254] Images retrieved from http://www.oipa.org/international/photo/vivisection_primates.htm and from https://www.thomasrecording.com/solutions/solution-primate.html

Review of Monsanto Studies

Monsanto *in Vitro* Absorption Study of Glyphosate by DTL (2010) - (MON 79545) 450 g/L Glyphosate SL Formulation (MON 79545)

In February 2010, the United Kingdom's Dermal Technology Laboratory, Ltd., (DTL) completed their Monsanto-commissioned laboratory study entitled "*In vitro* absorption of glyphosate through human epidermis" (MON 79545) wherein they investigated the absorption and distribution of glyphosate in three different herbicide formulations. For all three formulations, they concluded that the dermal absorption of glyphosate from exposure to the herbicide would be minimal and far less than 1%. The study specifically concluded that, for the high undiluted dose, "*the mean total amount of absorbed glyphosate was 0.0573 ug/cm^2 (**0.012%** of applied dose)*." For the 1 to 15.6 (28.8 g/L) dilution and 1 to 188 (2.4 g/L) dilution (consistent with spray applications), "*the mean total amounts of absorbed glyphosate were 0.379 and 0.021 ug/cm^2 (**0.129%** and **0.082%** of applied dose), respectively.*" In this study, glyphosate was removed from the surface of the epidermis by washing and then tape stripping. The amount of glyphosate on the epidermis after tape stripping, including that absorbed, was termed "potentially biologically available" and was determined to be 0**.049%, 0.796% and 0.245%** in order of increasing glyphosate formulation concentration.

However, there are serious problems with this study (as well as with other DTL studies) that contribute to inconsistency and, as a consequence, warrant the study's exclusion.

The design of the study included finite dosing of 10 µL/cm^2 which was used on a surface of 2.54 cm^2; this was left un-occluded for an exposure period of 24 hours with no interim wash. A static-type glass diffusion cell was used with dermatomed human skin. Each formulation was applied in three doses: one concentrated dose and two diluted doses. Thus, the amount of glyphosate in the 25.4 µL volume applied depended on the dilution. The absorption process was followed by taking samples of the receptor fluid (physiological saline) at recorded intervals throughout the exposure period.

Assessment of the DTL methodology reveals that 4,589 µg glyphosate acid/cm^2 was used in the formulation concentrate study and 293 µg glyphosate acid/cm^2 was used in the 1 to 15.6 dilution and 25 µg glyphosate acid/cm^2 was used in the 1 to 188 dilution study.

U.S. EPA guidelines for dermal testing recommend a maximum practical dose on the order of 1 mg/cm^2; larger doses can exceed saturation of the absorption process.[255] Thus,

[255] U.S. EPA OPPTS 870.7600, "Health effects test guidelines dermal penetration," August 1998, p. 4.

the formulation's concentration dose used *was not in compliance* and exceeded the threshold for maximum practical dose by a factor of 4.6.

DTL failed to properly follow OECD GD 28 (OECD, 2004c) regulations with respect to the definition and methodology that defines absorbed dose:

- The laboratory **did not always include** the glyphosate recovered from the tape stripping as they claimed that it was not biologically available.
- They also **did not always include** the amount of glyphosate recovered from stratum corneum (available for eventual absorption).

The "*In vitro* absorption of glyphosate through human epidermis" study presents itself as a pre-destined design failure. It is completely inconsistent with other previous Monsanto *in vitro* and *in vivo* studies and should be excluded as DTL violated OECD test regulations

Under "OECD guidelines for the testing of chemicals, Skin Absorption: *in vitro* Method 428," adopted April 13, 2004, "*The test substance remaining in the skin should be considered as absorbed unless it can be demonstrated that absorption can be determined from receptor fluid values alone*." Analysis of the other components (material washed off the skin and remaining within the skin layers) allows for further data evaluation including total test substance disposition and percentage recovery.

OECD GD 28 (OECD, 2004c) notes that, under certain circumstances, *in vivo* skin levels of the test compound need not be considered to be percutaneously absorbed.[256] This is appropriate where it can be demonstrated that test compound in the layers of skin at the end of a study will ultimately remain in the skin or be removed by the surface shedding of the stratum corneum.

However, for *in vitro* studies, OECD GD 28 notes that microcirculation is obliterated and the terminal stratum corneum levels may be elevated compared with *in vivo* levels. For these studies, OECD GD 28 states "…*it is therefore necessary that skin levels of test compound measured at the end of a study be included with the receptor fluid levels to determine total percutaneous absorption. Skin absorption may be expressed using receptor fluid alone provided that this can be justified*."

[256] OECD "Guidance notes on dermal absorption," Draft, October 22, 2010.

The current approach taken by nearly all regulatory agencies is to determine the dermal absorption value by adding the absorbed dose and the chemical remaining in the application site and surrounding skin following washing. This is appropriate for both *in vivo* and *in vitro* studies unless compelling evidence is presented that demonstrates that at least some portion of the residue in the skin is unlikely to be absorbed. However, there is currently some international disagreement about whether part or all of the test substance should be included in the dermal absorption value that is retained in the stratum corneum and can be removed by tape stripping.

For *in vivo* studies, it is widely accepted that, if absorption can be demonstrated as complete, then all or part of the chemical remaining in the skin may be considered as unavailable for absorption.

For *in vitro* studies, some regulatory authorities have a similar approach as for *in vivo* studies in that some of the amount retained in the skin may be considered as unavailable for systemic absorption.

Others would include all of the test substance retained in the skin following *in vitro* exposure. The following sections provide guidance to assist in the consideration of whether to exclude some portion of the residue in the skin.

Tape Stripping

OECD GD 28 states that skin fractionation may be conducted following exposure either *in vitro* or *in vivo* and notes that tape stripping can be difficult *in vitro* with epidermal membranes, rodent skin, study durations of more than 24 hours or where the test preparation alters the stratum corneum.

Test substance retained in the top few layers of the stratum corneum (*i.e.,* contained in the first few tape strips) may be removed by desquamation and therefore may not be absorbed. This includes substances retained in the top few layers of the stratum corneum as well as material that has not penetrated into the stratum corneum but is protected from wash-off (for example, in hair follicles or sweat ducts).

In the European Union and some other countries, it is the general practice to exclude the amount that was found in the first (upper) two tape strips at study completion both *in vitro* and *in vivo*.

Test substance in lower layers of the stratum corneum may penetrate into the dermis or may be removed by desquamation. Determination of the potential bioavailability of this test substance should be made on a case-by-case basis.

Dermal absorption is primarily a diffusion-driven process and therefore test substances in the lower layers of the stratum corneum should be assumed to form a reservoir that may become systemically available unless it can be demonstrated *in vivo* that absorption is complete and this test substance will remain in the stratum corneum until exfoliated.

Deviations or lack of documentation within the DTL (2010) studies include:

- Failure to include glyphosate remaining in the stratum corneum
- No documentation as to how the split-thickness skin measurement (typically 200-400 µm thick) is prepared.
- Although tape striping was performed, all of the layers were excluded from the "*mean total amounts of absorbed glyphosate*" at **0.012%**, **0.129%** and **0.082%** as reported.
- Tape stripping has only been discussed in the "Draft" 2010 OECD regulations and is limited to the first two tape strip extractions. Even if it were the official regulation, DTL deviated from the proposed methodology.

In summary, *"The current approach taken by nearly all regulatory agencies is to determine the dermal absorption value by adding the absorbed dose and the chemical remaining in the application site and surrounding skin following washing. This is appropriate for both in vivo and in vitro studies unless compelling evidence is presented that demonstrates that at least some portion of the residue in the skin is unlikely to be absorbed."* (OECD, "Guidance Notes on Dermal Absorption [draft]," October 22, 2010)

It is also critical to note that results of the 1 to 188 spray dilution MON 79545 dermal absorption study (0.082% absorbed) falls approximately 35 times below the prior 3% dermal absorption value established by the U.S. EPA and 54 times less than that of the 4.4% dermal absorption rate measured in primates in the Wester, et al., study (1991).

Monsanto *in Vitro* Absorption Study of Glyphosate by DTL (2010) - (MON 52276)

In February 2010, Dermal Technology Laboratory, Ltd., also completed their Monsanto-commissioned lab study entitled "*In vitro* absorption of glyphosate through human epidermis." For MON 52276 concentrate (undiluted dose), "*the mean total amount of absorbed glyphosate was 0.332 ug/cm^2 (0.009% of applied dose)*." For the 1 to 12.5

dilution and 1 to 150 dilution (consistent with spray applications), "*the mean total amounts of absorbed glyphosate were 0.086 and 0.023 ug/cm^2 (0.029% and **0.092%** of applied dose), respectively.*" Thus, compared to earlier (non-DTL) studies, results of the above MON 52276 high dose dermal absorption study fell approximately 103 times below the prior 3% dermal absorption value established by the U.S. EPA and 151 times less than that of the 4.4% dermal absorption rate measured in primates in the Wester, et al., study (1991). The MON 52276 diluted dose dermal absorption study fell approximately 33 times below the prior 3% dermal absorption value established by the U.S. EPA and 48 times less than that of the 4.4% dermal absorption rate measured in primates in the Wester, et al., study (1991).

Monsanto *in Vitro* Absorption Study of Glyphosate by DTL (2010) - (MON 79351)

Studies on MON 79351, also completed in February 2010, reported for the high undiluted dose that "*the mean total amount of absorbed glyphosate was 0.342 ug/cm^2 (**0.007%** of applied dose)*." For the 1 to 16.7 dilution (consistent with spray applications), "*the mean total amounts of absorbed glyphosate was 0.553 ug/cm^2 (**0.182%** of applied dose)*." Thus, compared to earlier (non-DTL) studies, results of the above MON 79351 high undiluted dose dermal absorption study fell approximately 16 times below the prior 3% dermal absorption value established by the U.S. EPA and 24 times less than that of the 4.4% dermal absorption rate measured in primates in the Wester, et al., study (1991).

The above studies were carried out under the direction of R.J. Ward. DTL is managed by Dave Fox who was previously the head of the *in vitro* percutaneous absorption group at Syngenta Central Toxicology Laboratory. (Syngenta is also a producer of glyphosate and seeds.)

The above DTL studies are vastly inconsistent and discrepant compared to all prior Monsanto glyphosate dermal absorption studies performed by non-DTL laboratories. The inexplicable differences in dermal absorption bioavailability unquestionably renders the study credibility as suspect and, as a consequence, warrants its exclusion.

Monsanto *in Vitro* Absorption Study of Glyphosate by DTL (2015) - (MON 76829) 72 g/L Glyphosate Gel Formulation

In April 2015, Dermal Technology Laboratory, Ltd., completed their Monsanto-commissioned lab study entitled "72 g/L Glyphosate Gel Formulation (MON 76829) - *In Vitro* Absorption through Human Dermatomed Skin using [^{14}C]-Glyphosate."

Human skin samples were obtained from the National Disease Research Interchange (NDRI, Philadelphia, Pennsylvania). Skin sections were cut at a thickness setting of 400 µm using an electric dermatome. It is not stated in the methodology whether tissues were also separated by heat.

The type of static glass diffusion cell used in this study had an exposed skin surface area of 2.54 cm^2 and a receptor volume of approximately 4.5 mL. Discs of approximately 3.3 cm diameter of prepared skin were mounted, dermal side down, in diffusion cells held together with individually numbered clamps and placed in a water bath maintained at 32°C ± 1°C. A nominal application rate of 10 µL/cm^2 or 720 µg glyphosate acid/cm^2 was reported.

DTL concluded that the highly concentrated gel formulation had a dermal absorption rate of glyphosate from exposure to the herbicide gel at 6, 8 and 10 hours of 0.013 µg/cm^2, 0.018 µg/cm^2 and 0.014 µg/cm^2, respectively. These respective amounts expressed as percentages of the applied dose were 0.002%, 0.003% and 0.002%. The mean amount penetrated over the entire 24 hour experimental period was 0.018 µg/cm^2 corresponding to **0.003%** of the applied dose. "*Practically all of the applied glyphosate acid (105%) was washed off the surface of the skin following the six hour exposure with a further 0.048% being removed at the 24 hour wash*." The proportions of the dose applied that were recovered from the donor chamber, stratum corneum (tape strips 1-5), and remaining skin were 0.042%, 0.003% and 0.009%, respectively. The proportions of the dose applied that were recovered from the donor chamber, stratum corneum (tape strips 1-5), and remaining skin were 0.042%, 0.003% and 0.009%, respectively. The bioavailability of glyphosate acid from this gel formulation was reported to be **0.011%** of the applied dose.

Assessment of the DTL methodology reveals that 720 µg glyphosate acid/cm^2 was used in this study. The U.S. EPA guidelines for dermal testing recommend a maximum practical dose on the order of 1 mg/cm^2; larger doses can exceed saturation of the absorption process.[257] Thus, the dose used was in compliance, but at the upper range (72% of the threshold).

It is not stated in the methodology whether tissues were also separated by heat and if so, what temperature or duration. Results of the MON 76829 gel dermal absorption study fall approximately 272 times below the prior 3% dermal absorption value established by the

[257] U.S. EPA OPPTS 870.7600, "Health effects test guidelines dermal penetration," August 1998, p. 4.

U.S. EPA and 400 times less than that of the 4.4% dermal absorption rate measured in primates in the Wester, et al., study (1991).

Most importantly, this study tested a glyphosate gel and did not include any surfactants which are typically a major component of Roundup formulations and allow for penetration of the formulation.

The study was carried out under the direction of Diane J. Davis who worked for Syngenta until 2007. As mentioned earlier, DTL is managed by Dave Fox who was previously the head of the *in vitro* percutaneous absorption group at Syngenta Central Toxicology Laboratory. (Syngenta is also a producer of glyphosate and seeds.) This DTL study is vastly inconsistent and discrepant compared to all prior Monsanto glyphosate dermal absorption studies performed by non-DTL laboratories. The inexplicable differences in dermal absorption bioavailability renders the credibility of this study of questionable merit and, as a consequence, warrants its exclusion.

Monsanto *in Vitro* Absorption Study of Glyphosate by DTL (2015) - (MON 76258) 7.2g/L Glyphosate Gel Formulation

In April 2015, Dermal Technology Laboratory, Ltd., also completed their Monsanto-commissioned lab study entitled "7.2 g/L Glyphosate Gel Formulation (MON 76258) - *In Vitro* Absorption through Human Dermatomed Skin using [^{14}C]-Glyphosate"

Human skin samples were obtained from the National Disease Research Interchange (NDRI**,** Philadelphia, Pennsylvania). Skin sections were cut at a thickness setting of 400 µm using an electric dermatome. It is not stated in the methodology whether tissues were also separated by heat.

The type of static glass diffusion cell used in this study had an exposed skin surface area of 2.54 cm^2 and a receptor volume of approximately 4.5 mL. Discs of approximately 3.3 cm diameter of prepared skin were mounted, dermal side down, in diffusion cells held together with individually numbered clamps and placed in a water bath maintained at 32°C ± 1°C. A nominal application rate of 10 µL/cm^2 or 720 µg glyphosate acid/cm^2 was reported.

DTL concluded that the gel formulation had a dermal absorption rate of glyphosate from exposure to the herbicide at 6, 8 and 10 hours of 0.005 µg/cm^2. These respective time points can be expressed as percentages of the applied dose; *i.e.,* 0.002%, 0.003% and 0.002%. The mean amount penetrated over the entire 24 hour experimental period was

0.006 µg/cm^2 corresponding to **0.008%** of the applied dose. "*Practically all of the applied glyphosate acid (103%) was washed off the surface of the skin following the six hour exposure with a further 0.211% being removed at the 24 hour wash*." The proportions of the dose applied that were recovered from the donor chamber, stratum corneum (tape strips 1-5), and remaining skin were 0.035%, 0.017% and 0.023%, respectively. The bioavailability of glyphosate acid from this gel formulation was **0.040%** of the applied dose.

Assessment of the DTL methodology reveals that 7.2 µg glyphosate acid/cm^2 was used in this study. The U.S. EPA guidelines for dermal testing recommend a maximum practical dose on the order of 1 mg/cm^2; larger doses can exceed saturation of the absorption process.[258] Thus, the dose used was in compliance at the upper range (7.2% of the threshold).

It is not stated in the methodology whether tissues were also separated by heat and if so, what temperature or duration. Results of the MON 76258 gel dermal absorption study fall approximately 75 times below the prior 3% dermal absorption value established by the U.S. EPA and 110 times less than that of the 4.4% dermal absorption rate measured in primates in the Wester, et al., study (1991).

Most importantly, this study tested a glyphosate gel and did not include any surfactants which are typically a major component of Roundup formulations and allow for penetration of the formulation.

As above, the study was carried out under the direction of Diane J. Davis who worked for Syngenta up to 2007. DTL is managed by Dave Fox who was previously the head of the *in vitro* percutaneous absorption group at Syngenta Central Toxicology Laboratory. This DTL study is vastly inconsistent and discrepant compared to all prior Monsanto glyphosate dermal absorption studies performed by non-DTL laboratories. The inexplicable differences in dermal absorption bioavailability renders the credibility of this study of questionable merit and, as a consequence, warrants its exclusion.

[258] U.S. EPA OPPTS 870.7600, "Health effects test guidelines dermal penetration," August 1998, p. 4.

Monsanto *in Vitro* Absorption Study of Glyphosate by DTL (2016) - (MON 76952) 500 g/L Glyphosate SL Formulation

During August 2016, Dermal Technology Laboratory, Ltd., also completed their Monsanto-commissioned lab study entitled "500 g/L Glyphosate SL Formulation (MON 76952) - *In Vitro* Absorption through Human Dermatomed Skin using [^{14}C]-Glyphosate"

Human skin samples were obtained from the National Disease Research Interchange (NDRI, Philadelphia, Pennsylvania). Skin sections were cut at a thickness setting of 400 µm using an electric dermatome. It is not stated in the methodology whether tissues were also separated by heat.

The type of static glass diffusion cell used in this study had an exposed skin surface area of 2.54 cm^2 and a receptor volume of approximately 4.5 mL. Discs of approximately 3.3 cm diameter of prepared skin were mounted, dermal side down, in diffusion cells held together with individually numbered clamps and placed in a water bath maintained at 32°C ± 1°C. A nominal application rate of 10 µL/cm^2 or 720 µg glyphosate acid/cm^2 was reported.

DTL concluded that the 500 g/L formulation concentrate had a dermal absorption rate of glyphosate with the mean amount penetrated over the entire 24 hour experimental period of 0.022 µg/cm^2 corresponding to 0.022% of the applied dose. The mean amount penetrated over the entire 24 hour experimental period was 0.512 µg/cm^2 corresponding to **0.010%** of the applied dose. Bioavailable dose was determined to be 0.088%.

With respect to the 1/500 w/v aqueous spray dilution after a small lag phase of 1 hour, *"practically no glyphosate was absorbed (0.0006 µg/cm^2/hour)."* The mean absorption rate of glyphosate acid through human dermatomed skin increased to 0.002 µg/cm^2/hour between 1-2 hours. This reduced to 0.0003 µg/cm^2/hour between 4-12 hours and 0.0001 µg/cm^2/hour between 12-24 hours. Over the 24 hour experimental period the mean absorption rate was 0.0003 µg/cm^2/hour.

The amounts of glyphosate acid that were absorbed through human skin at 6, 8 and 10 hours were 0.005 µg/cm^2, 0.006 µg/cm^2 and 0.006 µg/cm^2, respectively. These amounts expressed as percentages of the applied dose were 0.052%, 0.058% and 0.063%. The mean amount penetrated over the entire 24 hour experimental period was 0.008 µg/cm^2 corresponding to **0.081%** of the applied dose. Bioavailable dose was determined to be 0.200%.

Assessment of the DTL methodology reveals that 5,000 µg glyphosate acid/cm^2 and 10 µg glyphosate acid/cm^2 was used in this study. The U.S. EPA guidelines for dermal testing recommend a maximum practical dose on the order of 1 mg/cm^2; larger doses can exceed saturation of the absorption process.[259] Thus, the high dose used exceeded the threshold by five-fold.

It is not stated in the methodology whether tissues were also separated by heat and if so, what temperature or duration.

Results of the 500 g/L MON 76952 concentrate dermal absorption study fell approximately 300 times below the prior 3% dermal absorption value established by the U.S. EPA and 440 times less than that of the 4.4% dermal absorption rate measured in primates in the Wester, et al., study (1991).

Results of the spray dilution MON 76952 dermal absorption study fell approximately 37 times below the prior 3% dermal absorption value established by the U.S. EPA and 54 times less than that of the 4.4% dermal absorption rate measured in primates in the Wester, et al., study (1991).

There is no indication that surfactants are present in this glyphosate formulation.

As before, the study was carried out under the direction of Diane J. Davis who worked for Syngenta up to 2007. DTL is managed by Dave Fox who was previously the Head of the *in vitro* percutaneous absorption group at Syngenta Central Toxicology Laboratory. This DTL study is vastly inconsistent and discrepant compared to all prior Monsanto glyphosate dermal absorption studies performed by non-DTL laboratories. The inexplicable differences in dermal absorption bioavailability renders the credibility of this study of questionable merit and, as a consequence, warrants its exclusion.

Monsanto *in Vitro* Absorption Study of Glyphosate by DTL (2015) - (MON 76879) 360 g/L Glyphosate SL Formulation

During August 2017, Dermal Technology Laboratory, Ltd., also completed their Monsanto-commissioned lab study entitled “360 g/L Glyphosate SL Formulation (MON 76879) - *In Vitro* Absorption through Human Dermatomed Skin using [^{14}C]-Glyphosate”

Human skin samples were obtained from the National Disease Research Interchange (NDRI, Philadelphia, Pennsylvania). Skin sections were cut at a thickness

[259] U.S. EPA OPPTS 870.7600, “Health effects test guidelines dermal penetration,” August 1998, p. 4.

setting of 400 µm using an electric dermatome. It is not stated in the methodology whether tissues were also separated by heat.

The type of static glass diffusion cell used in this study had an exposed skin surface area of 2.54 cm^2 and a receptor volume of approximately 4.5 ml. Discs of approximately 3.3 cm diameter of prepared skin were mounted, dermal side down, in diffusion cells held together with individually numbered clamps and placed in a water bath maintained at 32°C ± 1°C. A nominal application rate of 10 µL/cm^2 or 720 µg glyphosate acid/cm^2 was reported.

DTL concluded that the 360 g/L formulation concentrate had a dermal absorption rate of glyphosate from exposure to the herbicide with the mean amount of 0.791 µg/cm^2 penetrated over the entire 24 hour experimental period and corresponding to 0.022% of the applied dose.

A 1/267 w/v aqueous spray dilution had a dermal absorption rate of glyphosate absorbed through human skin at 6, 8, 10 and 12 hours at 0.004 µg/cm^2, 0.004 µg/cm^2, 0.005 µg/cm^2 and 0.005 µg/cm^2, respectively. These amounts expressed as percentages of the applied dose were 0.029%, 0.033%, 0.035% and 0.037%. The mean amount penetrated over the entire 24 hour experimental period was 0.006 µg/cm^2 corresponding to **0.042%** of the applied dose.

"*Practically all of the applied glyphosate acid (102%) was washed off the surface of the skin following the six hour exposure with a further 0.375% being removed at the 24 hour wash.*" The proportions of the dose applied that were recovered from the donor chamber, stratum corneum and remaining skin were 0.080%, 0.032% and 0.111%, respectively.

The bioavailability of glyphosate acid from the spray dilution is the sum of the receptor fluid dose at 24 hours plus the amount remaining in the skin following tape stripping and tape strips 3-5. This was **0.162%** of the applied dose.

Assessment of the DTL methodology reveals that 3,600 µg Glyphosate acid/cm^2 and 13.5 µg glyphosate acid/cm^2 was used in this study. The U.S. EPA guidelines for dermal testing recommend a maximum practical dose on the order of 1 mg/cm^2; larger doses can exceed saturation of the absorption process.[260] Thus, the high dose used exceeded the threshold

[260] U.S. EPA OPPTS 870.7600, "Health effects test guidelines dermal penetration," August 1998, p. 4.

by 3.6 fold. It is not stated in the methodology whether tissues were also separated by heat and if so, what temperature or duration.

Results of the spray dilution MON 76859 dermal absorption study fall approximately 18.5 times below the prior 3% dermal absorption value established by the U.S. EPA and 27.5 times less than that of the 4.4% dermal absorption rate measured in primates in the Wester, et al., study (1991).

This MON 76879 commercial formulation is noted to contain a surfactant called Synergen GD2 at a volume of 4.78% w/w while glyphosate (pure acid and salt) was 60.63% w/w. For comparison, the ethoxylated tallowamine (POEA) surfactant in Roundup Classic is designated by Monsanto as MON 0818[261] and is a concentration that is typically reported as approximately 15% of the formulation weight to volume or 150 g/L.[262,263,264,265] Per Johan van Burgsteden's "*In vitro* percutaneous absorption study with [14C]-glyphosate using viable rat skin membranes," June 14, 2002, **Unaudited draft report** V4478 (TNO Dermal Penetration Study), MON 35012 is known to constitute glyphosate isopropylamine salt (46% w/w) and surfactant cocoamine (18% w/w), water and minor ingredients (35.5% w/w). In that study, penetration of glyphosate was found to range from 2.6% to 10.3%.

The DTL 2015 (MON 76879) study was carried out under the direction of Diane J. Davis who worked for Syngenta up to 2007. DTL is managed by Dave Fox who was previously the Head of the *in vitro* percutaneous absorption group at Syngenta Central Toxicology Laboratory. This DTL study is vastly inconsistent and discrepant compared to all prior Monsanto glyphosate dermal absorption studies performed by non-DTL laboratories.

The ***inexplicable differences*** in dermal absorption bioavailability render the credibility of this study of any questionable merit and, as a consequence, warrants its exclusion.

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[261] Monsanto response to the concern of the Slovenian authorities on the composition of the Plant Protection Product MON 79376 (360 g/ 1 glyphosate) and the surfactant MON 59117 (CAS n ° 68478-96-6). MONGLY02817577

[262] Id.

[263] Diamond, G., Durkin, P., "Effects of surfactants on the toxicity of glyphosate with specific reference to RODEO," 1997, Syracuse Research Corporation, SERA TR 97-206-1b.

[264] Giesey, J. P., Dobson, S., & Solomon, K. R., "Ecotoxicological risk assessment for Roundup herbicide," 2000, Rev. Environ. Contam. Toxicol. 167, pp. 35-120.

[265] Defarge, N. E., "Co-formulants in glyphosate-based herbicides disrupt aromatase activity in human cells below toxic levels, 2016, Int J Environ Res Public Health, Vol. 13(3), p. 264.

Effects of Temperature on Skin Used in Laboratory Experiments

A 1998 study[266] by Wester, et al., concluded that:

> "...human skin will sustain viability for 8 days following donor death in this system. Heat-treated (60°C water for one minute) and heat-separated epidermis and dermis **lose viability**.
>
> **Conclusions:** Human skin viability can be maintained for absorption studies. **It is recommended that** … **heat separation and skin freezing not be used** in absorption studies where skin viability and metabolism might be contributing factors to the study.
>
> "Dermatomed skin was heat-treated at 60°C for one minute to simulate the heat-separation procedure to produce epidermis separated from dermis (but no separation was performed) (Table 2). Lactate production decreased significantly ($p<0.000$; $p<0.04$) for both heat-treated skin samples. Therefore, **heating to separate epidermis from dermis damages viability**.
>
> "In another study [Table 3] lactate production was determined in heat-separated epidermis and dermis. The cumulative lactate production was much less than intact dermatomed skin, again showing the **detrimental effect of heat-separation on skin viability**."

These study citations clearly reveal that the outcomes of skin absorption tests can be influenced merely by choosing a particular skin preparation procedure. The profound differences in DTL results provide objective evidence that the laboratory may have engaged in such practices.

It is further noteworthy that with regard to changes that occur in skin when subjected to low temperatures, Mesager, et al., noted in a 2003 article[267] that:

> "Skin is complex and may display variable structural and metabolic change '*ex vivo*'. … Frozen samples showed some sign of stratum corneum fragmentation although this was not obvious. LDH activity measured in fresh samples kept at 4 °C was low, but it was stable up to 7 days. Fresh samples kept at 32 °C had a comparable LDH activity to the ones kept in the fridge up to 4 days. Frozen samples, thawed and then kept at 4 °C, showed a stable LDH activity after 24 h of incubation. However, frozen samples incubated at 32 °C demonstrated a high variability in results with up to 800 U/L of LDH activity after 5 days of incubation. … Although the measurement of enzyme activity was easy to perform and gave reproducible results, the use of single-enzyme activity (measuring only one pathway among the many metabolic pathways occurring within a cell) ***can be criticized when used on its own***."

Table 16 summarizes the available glyphosate dermal absorption studies.

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[266] Wester, et al., "Human Cadaver Skin Viability for *In Vitro* Percutaneous Absorption: Storage and Detrimental Effects of Heat-Separation and Freezing," 1998, Pharmaceutical Research, Vol. 15, No. 1.

[267] Messager, et al., "Assessment of skin viability: Is it necessary to use different methodologies?" Skin Research and Technology, December 2003, Vol. 9, pp. 321–330.

Table 16

Glyphosate Dermal Absorption Studies

Name/Author	Study Sponsor	Date	Specie	Design	Full Skin	Derma-tomed Skin	Stated % Dermal Absorption	% Absorption Including Unaccounted
Franz, *"Evaluation of the percutaneous absorption of three formulations of glyphosate"*	Monsanto	1983	Human	*in vitro*	Yes	Yes	0.028% MON0139 0.063% Roundup 0.152% Spray Mix	0.152% (fluid) plus 4.02% ("in epidermis") = 4.17% absorption
Study Notes: Study used unfrozen abdominal human skin obtained at autopsy; used radioactive glyphosate as labeled recovery target; failed to include unaccounted dose per OECD regulations; POEA of Roundup caused dermal absorption to increase by a factor of 2.25 due to the formulants in Roundup								
Maibach, "Elimination of 14C-glyphosate in Rhesus monkeys…"	Monsanto	1983	Primate	*in vivo*	Yes	No	1.80%	>1.8%
Study Notes: U.S. EPA guidelines require *that* at least 90% of dose be accounted for as compared to 16% in the Maibach study. U.S. EPA classified the study as unacceptable since the majority of dose was not correctly accounted for.								
Wester, *"Glyphosate skin binding, absorption, residual tissue distribution and skin decontamination."*	Monsanto	1991	Human, Primate	*in vitro* *in vivo*	Yes	No	4.4% (low dose) 2.9% (high dose)	22.6% (if bound and unaccounted amount added per OECP regulations)
Study Notes: Inappropriately large dose exceeded saturation; caused artificial reduction of percentage absorbed in test subjects. Additionally, study underestimates systemic dose from dermal absorption by a factor of 4.5 due to omission of fecal elimination. Authors state 18.2% was "lost." OECD regulations require bound or unaccounted dose to be added. Thus, 4.4% + 18.2% = 22.6%.								
Wester, "*In vitro* human skin absorption."	Monsanto	1991	Human	*in vitro*	-	-	2.2% (± 0.5%)	-
Study Notes: Internal documents record fact that Monsanto considered study results *"too risky"* to submit. Study discontinued by Monsanto prior to regulatory review; *results were never published.*								

Table 16

Glyphosate Dermal Absorption Studies

Name/Author	Study Sponsor	Date	Specie	Design	Full Skin	Derma-tomed Skin	Stated % Dermal Absorption	% Absorption Including Unaccounted
TNO Study: van Burgsteden, *"In vitro percutaneous absorption study [14C]-glyphosate using viable rat skin membranes"* (MON 35012)	Monsanto	2002	Rat	*in vitro*	-	-	2.6% ± 1.4 % (low dose) 10.3% ± 4.2 % (high dose)	Variable recovery Up to 18% absorption
Study Notes: Maximum penetration of 10.3 % occurred with the higher dose of MON 35012 concentrate which contained the surfactant Cocoamine; one test membrane absorbed approximately 18% of the applied dose.								
TNO Study (MON 0319) (70%)	Monsanto	2002	Rat	*in vitro*	-	-	1.4% ± 2.2 % (low dose) 1.3% ± 1.9 % (high dose)	Variable recovery
Study Notes: IPA salt of glyphosate only; no surfactant in test formulation. Wide range of statistical variability reported (more than 100%)								
DTL, *"450 g/L glyphosate in vitro absorption of glyphosate through human epidermis."* (MON79545)	Monsanto	Feb 2010	Human	*in vitro*	No	Yes	0.012% (high dose) 0.129% (med dose) 0.082% (low dose)	0.049% (high dose) 0.796% (med dose) 0.245% (low dose)
Study Notes: Bioavailability (i.e. (absorbed + epidermis after tape striping) was 0.049%, 0.796% and 0.245% in order of increasing glyphosate concentration applied. This would have been higher but the study excluded all glyphosate recovered from the stratum corneum. Study did not state tissue thickness. Manually teased away dermis following 60˚ emersion for 40-45 seconds. Failed to include stratum corneum quantities in total absorbed dose.								
DTL, *"360 g/L glyphosate in vitro absorption of glyphosate through human epidermis."* (MON 52276)"	Monsanto	Feb 2010	Human	*in vitro*	No	Yes	0.009% (high dose) 0.029% (med dose) 0.092% (low dose)	0.064% (high dose) 0.134% (med dose) 0.277% (low dose)

Table 16

Glyphosate Dermal Absorption Studies

Name/Author	Study Sponsor	Date	Specie	Design	Full Skin	Derma-tomed Skin	Stated % Dermal Absorption	% Absorption Including Unaccounted
Study Notes: Bioavailable percentage would have been higher but the study excluded all glyphosate recovered from the stratum corneum. When compared to earlier (non-DTL studies) high undiluted dose dermal absorption study this fell 333.33 times below the prior 3% dermal absorption value established by the U.S. EPA and 488.89 times less than that of the 4.4% dermal absorption rate measured in primates by Wester, et al. (1991). These inexplicable findings of vastly lower absorption values fail to note that the glyphosate formulation is essentially *unchanged* since earlier studies were conducted.								
DTL, *"480 g/L glyphosate in vitro absorption of glyphosate through human epidermis*" (MON79351)"	Monsanto	Feb 2010	Human	*in vitro*	No	Yes	0.007% (high dose) 0.182% (med dose) 0.048% (low dose)	0.123% (high dose) 0.262% (med dose) 0.799% (low dose)
Study Notes: The bioavailable amount in the low dose dilution was 0.8%, this amount excludes all glyphosate in the stratum corneum, and would have been higher. When compared to earlier (non-DTL studies), high undiluted dose dermal absorption study fell ~16 times below the prior 3% dermal absorption value established by the US EPA and ~24 times less than that of the 4.4% dermal absorption rate measured in primates by Wester, et al. (1991). These inexplicable findings of vastly lower absorption findings fail to note that the glyphosate formulation is essentially unchanged since earlier studies were conducted.								
DTL, *"72 g/L Glyphosate Gel Formulation - In Vitro Absorption through Human Dermatomed Skin using [^{14}C]-Glyphosate"* (MON 76829)	Monsanto	Apr 2015	Human	*in vitro*	No	Yes	0.003% ("applied dose")	0.011%
Study Notes: No surfactants were used in this study which is a typical component that helps with absorption in Roundup formulations. Study fails to state whether tissues were separated by heat and if so what temperature or duration. Results fall approximately 272 times below the prior 3% dermal absorption value established by the US EPA and 400 times less than that of the 4.4% dermal absorption rate measured in primates in the Wester study (1991). Study is vastly inconsistent and discrepant compared to all prior Monsanto glyphosate dermal absorption studies performed by non-DTL laboratories								

Table 16

Glyphosate Dermal Absorption Studies

Name/Author	Study Sponsor	Date	Specie	Design	Full Skin	Derma-tomed Skin	Stated % Dermal Absorption	% Absorption Including Unaccounted
DTL, *"72 g/L Glyphosate Gel Formulation (MON 76258) - In vitro Absorption through Human Dermatomed Skin using [^{14}C]-Glyphosate"*	Monsanto	Apr 2015	Human	*in vitro*	No	Yes	0.008% ("applied dose")	0.04%
Study Notes:	No surfactants were used in this study which is a typical component that helps with absorption in Roundup formulations. Tissue cut @ 400 µm thickness via electrical dermatome; no implication whether tissue was heated; tissue was stored frozen at -20 ˚C. Complete amounts of recovered glyphosate in stratum corneum were not included.							
DTL, *"500 g/L Glyphosate SL Formulation - In vitro Absorption through Human Dermatomed Skin using [^{14}C]-Glyphosate,"* (MON 76952)	Monsanto	Aug 2016	Human	*in vitro*	No	Yes	0.010% (high dose) 0.081% (diluted dose)	0.088% (High dose) 0.200% (diluted dose)
Study Notes: 5,000 µg glyphosate acid/cm^2 and 10 µg glyphosate acid/cm^2 used. U.S. EPA guidelines for dermal testing recommend a maximum practical dose on the order of 1 mg/cm^2; larger doses can exceed saturation of the absorption process. Thus, the high dose used exceeded the threshold by a factor of 5. Tissue cut @ 400 µm thickness via electrical dermatome; no implication whether tissue was heated; tissue was stored frozen at -20 ˚C. There is no indication that surfactants are present in this glyphosate formulation.								
DTL, *"360 g/L Glyphosate SL Formulation (MON 76258) - In vitro Absorption through Human Dermatomed Skin using [^{14}C]-Glyphosate"*	Monsanto	Aug 2017	Human	*in vitro*	No	Yes	0.022% (high dose) 0.042% (diluted dose)	0.277% (high dose) 0162% (diluted dose)
Study Notes: Study results fall approximately **18.5 times below** the prior 3% dermal absorption value established by the US EPA and **27.5 times less** than that of the 4.4% dermal absorption rate measured in primates in the Wester study (1991). Tissue cut @ 400 µm thickness via electrical dermatome; no implication whether tissue was heated; tissue was stored frozen at -20˚C. Surfactants use is at a percentage lower that typical/classic glyphosate formulations								

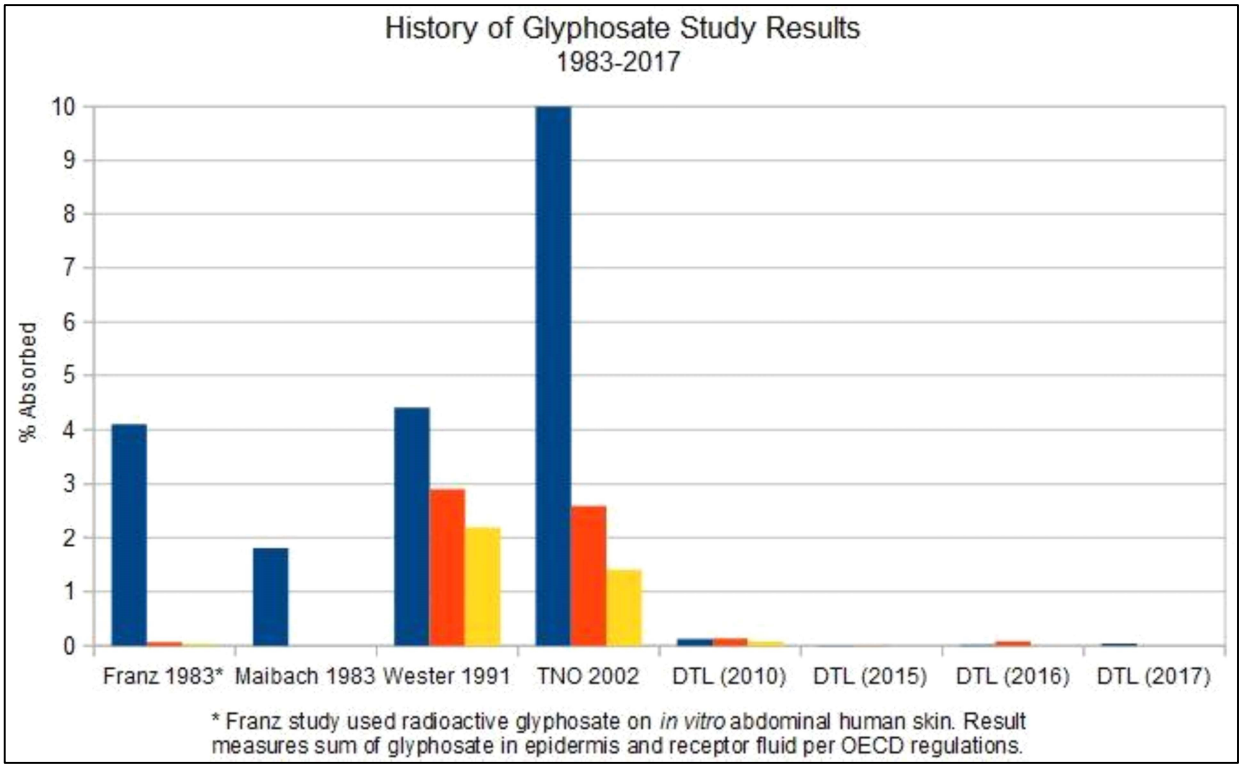

Figure 16: Historical Dermal Absorption Factors by Study[268]

Blue = Total % absorbed if unaccounted glyphosate added per OECP regulations
Red = Stated Low dose % absorbed
Yellow = Stated High dose % absorbed

The study compilation presented in **Table 16** reveals a remarkable finding. As shown in **Figure 16**, something "unexplained" appears to have happened in 2010. Monsanto made no significant alterations in product formulations, yet glyphosate dermal absorption inexplicably **dropped** – *by more than two orders of magnitude.*

This extraordinary event may be explained by the fact that the results for each year (2010, 2015, 2016, 2017) were produced by the same laboratory ("DTL"). As no other evident changes in product formulation occurred, it is evident that procedures and methodology at DTL have impacted the results and as previously noted, DTL failed to apply "Triple Pack" methods to validate their *in vitro* laboratory tests.

[268] Wester used Roundup which contained surfactants; Maybach's dermal absorption was radio labeled glyphosate dissolved in Roundup which contained surfactants and water; TNO study formulation also contained surfactants.

The DTL establishment was contracted by Monsanto and managed by a gentleman who was previously in charge of the *in vitro* percutaneous absorption group at Syngenta Central Toxicology Laboratory – who is also a producer of glyphosate and seeds.

Studies, Reviews & Articles Impacted by Wester and Maibach Studies

Inasmuch as there are numerous, highly significant flaws in the two Monsanto-sponsored studies, it is important to understand the impact these have had on other studies, reviews and published articles (some of which were authored by Monsanto consultants).

1. Williams, GM, Kroes, R., and Munro, IC, "Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans," 2000, Regulatory Toxicology and Pharmacology. Vol. 31, pp. 117–165.

   The Williams, et al., risk assessment article opined that the dermal penetration of glyphosate is very low based on results from studies in Rhesus monkeys and *in vitro* studies with human cadaver samples. With respect to the Wester studies, Williams failed to acknowledge the documented fecal elimination route and only relied on urinary excretion. Additionally, Williams, et al., failed to note the difference in fecal versus urinary excretion dependent upon dose level including the extraordinarily high dose level of pure product on the skin of primates within the Wester studies.

   The Williams, et al., review stated,[269] "*Maibach (1983) studied the in vivo dermal absorption of glyphosate when undiluted Roundup herbicide was applied to the skin of monkeys. Penetration was slow as only 0.4 and 1.8% of the applied dose was absorbed over 24 hours and 7 days, respectively. A second study in Rhesus monkeys investigated the absorption of diluted glyphosate (1:29) to simulate a spray solution (Wester, et al., 1991). Dermal penetration was found to be 0.8 and 2.2% at low and high dose (500 or 5,400 mg/cm^2, respectively). Wester, et al. (1991) also reported that the in vitro percutaneous absorption of glyphosate through human skin was no more than 2% when applied for up to 16 hours either as concentrated Roundup or as a diluted spray solution*."

2. Niemann, Lars, et al., "A critical review of glyphosate findings in human urine samples and comparison with the exposure of operators and consumers," 2015, Journal für Verbraucherschutz und Lebensmittelsicherheit, Vol 10, Issue 1, pp. 3-12.

[269] Williams, pp. 123-124.

The basic assumption in Niemann, et al., is that dermally absorbed glyphosate is eliminated nearly entirely through urine and that "*measuring of urine levels could be a powerful tool for human biomonitoring*." The study fails to reference or acknowledge the Wester and Maibach studies and does not consider dermally absorbed glyphosate at low, steady state rates of absorption being metabolized and excreted primarily through the feces.

Niemann, et al., states "*For active substances in plant protection products (PPP) with well-defined urinary elimination, no potential for accumulation and virtually no metabolism, measuring of urine levels could be a powerful tool for human biomonitoring. Such data may provide reliable estimates of actual internal human exposure that can be compared to appropriate reference values such as the 'acceptable daily intake (ADI)' or the 'acceptable operator exposure level (AOEL)'*."

Based on the Wester (1991) study, the evidence of "*well defined urinary elimination*" has been compromised. Such an assumption is misleading and potentially dangerous with respect to the human health risk assessment and comparisons to current ADI or the AOEL regulatory levels. Studies cited by Niemann, et al., include non-dermal dose assessments such as male SD rats receiving oral dosing (Brewster, et al., 1991),[270] oral dosing in feed (Chan & Mahler, 1992)[271] and IV and oral doses in rats (Anadon, et al., 2009).[272] None of the cited studies involve dermal dosing and **do not** establish "*well defined urinary elimination*" which is simply assumed. Furthermore, the Brewster study found that urine and feces were equally important routes of elimination and after 7 days, the total body burden (~1%) of the dose administered was mostly in bone. Since dermal glyphosate exposure is the primary route of exposure contributing to systemic exposure in agricultural users, the assumption that distribution, metabolism, and excretion are identical by IV and dermal routes of exposure leads to **egregious errors** in systemic dose calculations.

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[270] Brewster, D.W., Warren, J., and Hopkins, W.E., "Metabolism of glyphosate in Sprague-Dawley rats: Tissue distribution, identification, and quantitation of glyphosate-derived materials following a single oral dose," July 1991, Fundamental and Applied Toxicology, Volume 17, Issue 1, pp. 43-51.

[271] Chan, P. and Mahler, J., "Glyphosate (CAS No. 1071-83-6) administered in dosed feed to F344/N rats and B6C3F1 mice," 1992, U.S. Department of Health and Human Services. NTP Technical Reports Series No. 16. NIH Publication 92-3135.

[272] Anadón, A. et al., "Toxicokinetics of glyphosate and its metabolite aminomethyl phosphonic acid in rats," 2009, Toxicol Lett 190(1), pp. 91-95.

3. Acquavella, J., et al., "Glyphosate biomonitoring for farmers and their families: results from the Farm Family Exposure Study,"2004, Env. Health Perspect 112, pp. 321–326.

In an internal Monsanto document entitled, "Glyphosate Stewardship, Epidemiology and the Farm Family Exposure Study," Monsanto scientists report the study impetus:

> "We have been working to maintain glyphosate's favorable reputation through a strategy that anticipates challenges and puts appropriate initiatives in place. One of those initiatives is a unique research program called the Farm Family Exposure Study (FFES)." [273]

The report further states:

> "The FFES was developed to fill two data gaps. First, there is (PPE) information about applicator pesticide exposure under "real world" conditions. Second, there is little empirical exposure information for farm children although children's health is a driving force in environmental regulation and a focus of epidemiologic research." [274]

The "FFES" is a biomonitoring study which evaluated urinary glyphosate concentrations for forty-eight farm families (farmers, spouses and their children) the day before, the day of and three days after a glyphosate application. The authors used the urinary concentrations to estimate systemic doses which they then compared to the U.S. EPA reference dose of 2 mg/kgBW/day.

The main assumption in their analytic method is *"pharmacokinetic research indicates that absorbed glyphosate is excreted unchanged, predominantly in urine* (Williams 2000)."[275] Unfortunately, glyphosate is <u>not</u> excreted predominately through the urine in primates, especially at low doses, as demonstrated by the Wester, 1991, study.

The authors used the 95% urinary recovery that Wester reported using IV dosing to correct their data for complete pharmacokinetic recovery. This correction factor is not applicable to this data since the farmers and their family members were presumably exposed *dermally* and not through IV dosing.

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[273] "Glyphosate Stewardship, Epidemiology and the Farm Family Exposure Study," MONGLY00905651.

[274] Id, MONGLY00905652.

[275] Acquavella, J., et al., "Glyphosate biomonitoring for farmers and their families: results from the Farm Family Exposure Study," 2004, Environ Health Perspect, 112, pp. 321–326.

Monsanto also points out the limited degree of accuracy of their urinary glyphosate measurements in the Acquavella, et al., 2004, biomonitoring study:

> "Monsanto's analytic chemistry expertise was essential to the FFES. However, **our current method is outdated**. It requires relatively large volumes of urine (100 ml, versus 5 ml for the 2,4-D and chlorpyrifos methods) and produces less precise results than methods for other FFES chemicals. Given the likelihood that human health allegations will continue to surface for glyphosate, it seems advisable to invest in modernizing the analytic method to increase analytic flexibility and precision."[276]

4. Solomon, K., "Glyphosate in the general population and in applicators: a critical review of studies on exposure," 2016, Critical Reviews in Toxicology, 46(1), pp. 21-27.

   In the Solomon, 2016, review, it is again assumed that "*the systemic dose of glyphosate can be estimated from the total amount of glyphosate excreted in the urine over the four or five days following and including the day of application*." A "*correction for incomplete excretion*" of 95% is made "*based on observations in TK*[277] *studies in monkeys which showed that 95% of total systemic dose was excreted via urine (Wester, et al., 1991), divided by 0.95*."[278] Solomon does not consider dermally absorbed glyphosate at low, steady state rates of absorption being metabolized and excreted primarily through the feces.

5. Monsanto's Spanish "OPEX" biomonitoring study entitled "MON 78294: An Applicator Exposure Study Conducted in Spain," Autumn 2005.

   This study was conducted in order to estimate a systemic dose for occupational users of glyphosate and determine whether certain uses of the product resulted in unacceptable levels of dermal penetration. Monsanto submitted results of the studies to Spanish regulatory authorities as part of the herbicide registration process. A report was prepared for submission to the U.S. EPA, but it is unclear if it was ever submitted. In their determination of the systemic dose, they extrapolated the Wester, et al., 1991, study results to their biomonitoring data. As in the other examples cited above, doing so invalidates their values of the estimated systemic dose.

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[276] "Glyphosate Stewardship, Epidemiology and the Farm Family Exposure Study", MONGLY00905655.

[277] TK is an abbreviation for toxicokinetic and is used here as a synonym for pharmacokinetic.

[278] Solomon, K., "Glyphosate in the general population and in applicators: a critical review of studies on exposures," 2016, Critical Reviews in Toxicology, 46(1), pp. 21-27.

Regulatory Guidance on Dermal Absorption and Recovery

Either knowingly or unknowingly, Monsanto regularly misstates or understates glyphosate dermal absorption recovery and factors in its communications. It is not the purpose of this toxicological risk assessment to draw conclusions about the intent of such misstatements. However, it is helpful to understand the position of regulatory agencies on these points and to briefly review some key guidelines pertinent to this issue.

OECD: 18-Aug-2011 GUIDANCE NOTES ON DERMAL ABSORPTION Series on Testing and Assessment No. 156

The current default approach taken by nearly all regulatory agencies is to determine the dermal absorption value by adding the absorbed dose and the chemical remaining in the skin, following washing. This is appropriate for both *in vivo* and *in vitro* studies unless compelling evidence demonstrates that some portion of the residue in the skin is unlikely to be absorbed. OECD TG 427 and 428 (OECD 2004a and 2004b) require a mean mass balance recovery of the test substance of between 90–110%. The OECD GD28 (OECD 2004c) contains the same recommendation with a caveat that for volatile test substances and unlabeled test substances, a range of 80–120% is acceptable. However, with the *in vivo* study design, recoveries outside this range may be acceptable but must be justified.

The criteria to justify mean mass balance recovery values outside the acceptance range can be summarized by the following examples:

1. **Recovery values exceed the recommended range**: If the recoveries exceed the accepted maximum range, the data generated should not be normalized because that would result in potentially underestimated absorption values. If these absorption values are not acceptable when a risk assessment is conducted, then the study should be repeated to address any bias resulting from excessive recoveries.

2. **Recovery values below the recommended range**: Low recoveries raise the concern that the value for absorbed dose could be lower than that which would be achieved from a study where the recoveries were within the guideline range. The reason for low recovery may be attributable to the following factors: (a) incomplete application of dose, (b) loss to the experimental equipment, (c) incomplete extraction from matrices (or incomplete collection of exhaled CO_2), (d) evaporation, (e) unlabeled test preparations, metabolism or degradation or (f) insufficiently high analytical LODs/LOQs, in particular where non-labelling analytical methods are applied.

Monsanto Communications with Respect to Pharmacokinetics

During the glyphosate registration process in Spain, the Spanish Ministry of Health advised Monsanto of errors in their "OPEX" study. Faced with denial of Spanish product registration, Monsanto employees communicated concerns regarding pharmacokinetics of glyphosate. The following excerpts summarize some of the Monsanto communications.

A. Communication of [redacted] (11-4-2008): Subject: Pk (Pharmacokinetics) recovery, Wester, et al.

> "The IV data gives *in vivo* disposition of a systemic available dose. This dose could be the result of aggregate systemic exposure (meaning a systemic dose after combined oral, dermal, inhalation exposure). The total accountability of this experiment is high >96% - ~100% and we know exactly the amount that was systemically available. The recovery factor for urine is therefore relevant and reliable." [279]

Notably, the dose was not an "*aggregate systemic exposure*" as stated, but the result of an IV "push" injection. This is clearly stated in the study. Thus, one cannot conclude that the recovery factor from IV dosing is "*relevant and reliable*" to dermal dosing. It is critical to note that IV administration presents a **tremendously high acute dose** to the liver. Saturation of the liver as an elimination pathway to the feces would result in spill over to the urinary excretion elimination pathway. Giving the same (IV) dose quantity over a slow drip period of 24 hours would not expose the liver to potential saturation. The email conversation further states:

> "The *in vivo* dermal absorption experiment yielded variable results and much lower total accountability 77-82% which is normal for this kind of experiment. The authors take the outcome of the IV experiment to justify the use of the urinary excretion results from the topical experiment **only** as an estimate for dermal uptake. 'Since all of the IV administered doses were excreted in urine, the percutaneous absorption of glyphosate is estimated to be 0.8-2.2% of the applied dose' (p 728-729). They did not take the feces into account based on the IV study." [280]

Monsanto employee [redacted] did not take hepatic excretion through the feces into account and relied solely on the IV study. This omission produced **acutely high blood levels** not comparable to those achieved through slow, steady-state dermal absorption. Additionally, the erroneous urinary recovery assumption that Monsanto used

[279] MONGLY02155831.

[280] Id.

to correct the systemic dose is in grave error by a factor of 4.5 and, therefore, is in no way a *"good estimate."*

B. Communication of [redacted] (11-4-2008, response to [redacted] Subject: Pk recovery, Wester, et al.

> "Many thanks for your help which I will try to defend as Monsanto position, but the authorities will decide next week. That means they are now doing the homework- if our proposed safety evaluation for CAYENNE formulation is compatible with the Acceptable Operating Exposure Level (AOEL) for glyphosate. I imagine we do not have other studies on the urine/feces excretion after topical applications of glyphosate to support our position. **As it is critical that we have our product accepted in this coming meeting**, I would like to complete my defense with a paragraph like this one:
>
> "Although we believe that the intravenous dose is accepted by toxicology peer reviewers as the best indicator to simulate the systemic presence of glyphosate, in case the Spanish authorities consider that the excretion through the urine should be taken from the **variable data** reported in the topical administration (urine/urine + feces = 75.86% or 18.18%), the average excretion in the urine of 47.02% would mean that our final exposure values should be multiplied by 2.13 resulting in exposure levels which are well below the AOEL of 0.2 mg/kgBW/day." [281]

Several documents and in-house Monsanto studies report that the IV model is the best indicator as to how systemically-administered glyphosate is metabolized and excreted. This statement is <u>inaccurate</u> since it is the dermal systemic dose that is of primary interest to both toxicologists and regulatory authorities.

There are no reports of applicators intravenously injecting themselves with glyphosate. In the absence of actual primate dermal absorption data, the IV model should have been compared to animal models with urinary and fecal measurements conducted.

However, *it is not an acceptable practice in toxicology* to replace real *in vivo* data with a "model" unless the actual dermal dosing data was faulty. <u>There is no evidence to support this</u>. Monsanto's "variable data" problem has been used to avoid the finding of the alternate fecal elimination pathway. The "high variability" issue has been mis-applied in order to dismiss the primate dermal absorption test results. Monsanto has

[281] MONGLY02155830.

dismissed the primate data by failing to disclose why the "variable data" was excessive.

The variability of the data (*i.e.*, the percentage of urinary versus fecal elimination) was due to absorption saturation at the high dose as described previously and, therefore, only the low dose is relevant since it is closer to real-world exposure scenarios. Thus, the exposure values should be multiplied by **5.50,** not 2.13.

C. Communication of [redacted] (11-5-2008, response to All): Subject: Pk recovery, Wester, et al.

> "Even though we can absorb additional 'uncertainty factors' in our risk assessment based on our biomonitoring results, I feel uncomfortable with this discussion. This approach by Spain sets a precedent and **contradicts the fact that we always claimed to fully understand the glyphosate pharmacokinetics**. The Wester IV experiment suggests that almost the entire 'systemically' available dose was excreted in urine. The low dose topical *in vivo* experiment suggests that almost the entire dose (82%) that was absorbed through the skin was excreted in feces (3.6% feces versus 0.8% in urine). We should have a robust and well-documented explanation for this and stick to our original risk assessment or develop additional data to fully understand this matter and adjust our systemic dose calculations accordingly." [282]

D. Communication of David Saltmiras (11-4-2008, response to [redacted] Subject: Pk recovery, Wester, et al.

> "[redacted] Donna & I have discussed your approach and you are correct. How much below the AOEL are your calculations? Christophe - by our rough calculations, [redacted] approach is approximately 50x below the AOEL of 0.2 mg/kgBW/day, Even if we applied the 90th percentile for the passive dosimetry numbers, we would be below the AOEL." [283]

The pharmacokinetics assumed to be correct using the IV methodology are contradicted by the primate dermal absorption studies. [redacted] states *"This approach by Spain sets a precedent and contradicts the fact that we always claimed to fully understand the glyphosate pharmacokinetics."* He cites the discrepancy in the Wester study and the need to further investigate in order to fully understand the pharmacokinetics (and thereby "adjust" systemic dose calculations).

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[282] Id.

[283] MONGLY02155829.

E. Response communication of [redacted] (11-10-2008, response to All): Subject: Pk recovery, Wester, et al.

> "To fully address this issue would likely require a repeat of the monkey dermal and intravenous studies. We no longer own the custom-designed monkey chairs that prevented exfoliated abdominal skin from contaminating the excreta. Additionally, it is not clear whether similar chairs are used anymore by any researcher or if they would even be allowed. Thus, conducting a new series of monkey studies may not be easy nor inexpensive. Furthermore, it is not clear to me that such a study is necessary and would be **totally without risk**. Should we arrange a conference call to discuss this?"[284]

F. Communication of [redacted] (11-10-2008, response to team): Subject: Pk recovery, Wester, et al.

> "To me, all this discussion continues to show that we still need solid data for ADME (Absorption, Distribution, Metabolism and Excretion) arising from dermal exposure.
>
> 1. Our dermal absorption endpoint is based on the literature and, as I recall, we failed to get the original data to support the results.
> 2. The movement of glyphosate in the blood flow from dermal contact is different to that through oral or intravenous exposure. The little data we have suggests that the excretion is significantly more through the feces than the urine.
> 3. Dermal exposure is the greatest risk of exposure for operators. Therefore, we need to be secure on the ADME of such exposure.
> 4. The WHO and EU reviews focus on the IV and oral but not the dermal. My position is, therefore, unchanged. We need to address this properly in the Annex II dossier and, therefore, should be considering a study.[285]

As stated by [redacted], the movement of glyphosate in the blood flow from dermal contact is different to that through oral or intravenous exposure. It is precisely because such differences exist that clinical researchers (and toxicologists) apply published study findings according to the guidance provided.

[redacted] also notes that the study evidence has documented that glyphosate excretion is significantly more through the feces than the urine. This finding is highly

[284] MONGLY02155826.
[285] MONGLY02155827.

significant as it directly contradicts a key assertion found in many of Monsanto's published study results that elimination through urine alone accounts for the majority of recovery. Thus, this assumption can impact the results and accuracy of dermal absorption studies and biomonitoring studies of workers who have their urine tested.

G. Communication of [redacted] (11-12-2008, response to [redacted]
Subject: Pk recovery, Wester, et al.

> "Monsanto is a company with recurring discussions (which is good!)... You will remember that we discussed this in length with a lot of people before we initiated the Spanish OPEX study... (please see attached). The outcome was that (1) other animal data confirmed the Wester findings; (2) such a study would **be too risky** (potential for finding another mammalian metabolite); and (3) we would wait for the evaluation of Spain. Looking forward to this discussion on the 24th of November. I also recall that David has asked 2 external pharmacologists for an opinion on the Wester study. Would that opinion be available by that time?"[286]

The charge and responsibility of the toxicologist is to determine the ADME (absorption, distribution, metabolism and excretion) as ADME are critical components in the risk assessment process.

It is always of great importance to identify all metabolites since certain chemicals have been known to produce toxic metabolites under high dose levels (such as Tylenol) or carcinogenic metabolites (such as metabolites of benzene). Failing to perform a needed study due to the risk of finding an adverse result that could negatively impact unrelated agendas represents an unacceptable practice in the field of toxicology.

Factors Intensifying Dermal Absorption of Glyphosate

Beyond the underestimation of dermal absorption by Monsanto, there are additives within Roundup formulations that further increase dermal absorption of glyphosate and also enhance genotoxicity (for example, POEA derivatives).

There are numerous factors governing the rate and degree of dermal absorption, both intrinsically and potentially. In glyphosate, these include (a) "co-formulants" (ingredients other than the active ingredient such as detergents or anti-foam agents), (b) surfactants (compounds which lower surface tension), (c) humectants (to inhibit moisture loss), (d) adjuvants (chemicals which modify the effect of other agents), (e) absorption enhancement due to skin damage, lesions, cracks and other irregularities, (f) lack of

[286] MONGLY02155826.

personal protective gear and (g) other factors such as penetration enhancers and skin creams. This section reviews and assesses these factors as toxicological considerations.

Generally speaking, with the exception of substances of a proprietary nature or which have not been disclosed by Monsanto, most of the considerations mentioned above tend to intensify absorption rather than reduce it. The following sections review each factor individually given the limited information available at this time.

Co-Formulants

The exact identities and amounts of the co-formulants in GBF herbicides are usually unknown as they are kept as confidential trade secrets. In many countries (including the U.S.), manufacturers are only required to identify the declared active ingredient (DCI), *i.e.,* glyphosate. The co-formulants (*i.e*., all ingredients other than the DCI) have rarely been identified and have often been declared as "inert ingredients."[287]

Herbicide manufacturers frequently take advantage of regulatory agency definitions of "inert ingredients." Despite their name, inert ingredients may be biologically or chemically active and are labeled inert only because of their function in the formulated product. For example, an herbicide ingredient can be considered "inert" if it has no direct effect on the intended target, *i.e.,* the weed. In herbicides, the ingredients added to enhance absorption, increase ionization, prevent foaming or reduce drifting are characterized by the manufacturer as "inert ingredients" since they do not directly kill the weeds. However, they are not necessarily without toxicity to animals or humans.

Independent studies of complete herbicide formulations are not generally possible as specific herbicide formulations are protected. Manufacturers of co-formulants have been historically unwilling to provide them to scientists who wish to assess toxicity. Consequently, most co-formulants have evaded scientific scrutiny and regulation.

In a confidential draft report dated July 2001 entitled, "Clustering glyphosate formulations with regard to the testing for dermal uptake," Monsanto scientist [redacted] stated:

[287] Defarge, N. et al., "Co-formulants in glyphosate-based herbicides disrupt aromatase activity in human cells below toxic levels," 2016, Int J Environ Res Public Health, Vol. 26;13(3), pii: E264.

> "Glyphosate has a whole series of different formulations. The differences between those formulations are based on:
> - The different salt types used to formulate the active ingredient
> - The use of different surfactants
> - The active ingredient/surfactant ratio
> - The concentrations of active ingredient and surfactants
> - The presence or absence of other inert ingredients such as anti-foam agents.

He also added:

> Until today, Monsanto has conducted formulation specific dermal uptake research only on the formulation Roundup (MON2139). It is clear that because of the compositional differences, the dermal uptake data for Roundup can't be extrapolated as such towards the wide range of formulations. Every ingredient in a formulation can have a specific influence of dermal uptake. **Scientific experimental evidence is necessary**."

Detergents in herbicides act as mediators which change the absorption by increasing bioavailability[288] or by affecting the skin barrier function.[289,290] Brand and Mueller (2002) showed dermal penetration of commercially-formulated compounds was significantly greater ($p < 0.05$) than that of pure compounds at the same concentration.[291]

Surfactants

Like co-formulants, the exact identities and amounts of surfactants in GBF herbicides are usually unknown as they are kept as confidential trade secrets. The most predominately used surfactants in GBFs are polyoxyethylene alkylamine (POEA) surfactants.[292,293]

POEA is an acronym, not a specific chemical, which encompasses a wide range of alkyl-amine ethoxylate compounds. Within the group of POEA surfactants, the chemistry is

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[288] Sartorelli, et al, 1997.

[289] Treffel, P. & Gabrad, B., "Skin penetration and sun protection factor of ultraviolet filters from two vehicle," 1996, Pharmaceut Res, Vol. 13, pp. 770-774.

[290] Tupker, R. et al., "Susceptibility to irritants: role of barrier function, skin dryness and history of atopic dermatitis," 1990, *BJD.* Volume 123, Issue 2, pp. 199–205.

[291] Brand, R.M. & Mueller, C., "Transdermal penetration of atrazine, alachlor, and trifluralin: effect of formulation," 2002, Toxicol Sci., Vol. 68(1), pp. 18-23.

[292] Williams, G., et al., "Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans," 2000, Regulatory Toxicology and Pharmacology, Vol.31, pp. 117 - 165.

[293] Diamond, G., Durkin, P., "Effects of surfactants on the toxicity of glyphosate with specific reference to RODEO," 1997, Syracuse Research Corporation, SERA TR 97-206-1b.

complex and varied. Ethoxylated tallowamine has been the traditional surfactant component and the most well-known 'inert' ingredient contained in the original Roundup formulation and many others. It is a POEA non-ionic surfactant consisting of beef tallow fatty acid-derived alkyl chains converted to primary amines and ethoxylated with between 10 to 20 ethylene oxide (EO) units.[294] It is often mixed with polyethylene glycol or other surfactants plus other materials to facilitate manufacturing and formulation stability.[295] Roundup's surfactants include 1,4-dioxane (a probable human carcinogen) as an impurity at about 0.03%.[296]

POEA significantly increases penetration in plant cells as well as in animal cells. Richard, et al., found that the addition of surfactants "greatly facilitated" the penetration of glyphosate through animal cell membranes.[297]

It is helpful to understand that, due to corporate secrecy and proprietary concealment, POEA was first recognized as a common ingredient in herbicides in the 1980's when physicians in Japan reported that morbidity and deaths of patients who drank Roundup were due to POEA, not glyphosate.[298]

POEA is an eye irritant, toxic to aquatic organisms, penetrates cell membranes and disrupts their structure and function. Diamond and Durkin made the following observations regarding surfactants in glyphosate-based formulations:

1. **Multiple Formulations**: The formulations are chemical mixtures and must be considered as mixtures in toxicity assessments. In this context, an assessment of the specific surfactants in any of the formulations or generalizations about the toxicology of surfactants as a group may not apply to the formulations. This consideration places extreme importance on data regarding the toxicity of the

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[294] From an internal Monsanto report, Surfactant Issue Analysis, Issue: Increasing public attention to the POEA (Polyoxyethlene alkylamine) surfactant component of glyphosate formulations in connection with claims of adverse impact to aquatic life (recently, amphibians) and human health (*in vitro* cell culture toxicity tests). MONGLY01700591.

[295] Id.

[296] Monsanto, 1990 in Diamond, G., Durkin, P., "Effects of surfactants on the toxicity of glyphosate with specific reference to RODEO," 1997, Syracuse Research Corporation, SERA TR 97-206-1b.

[297] Richard, S., et al., "Differential effects of glyphosate and Roundup on human placental cells and aromatase," 2005, Environmental Health Perspectives.

[298] Sawada, Y., Nagai, Y., Ueyama, M., and Yamarnoto, I., "Probable toxicity of surface active agent in commercial herbicide containing glyphosate," 1988, Lancet 1 (8580), p. 29.

formulations themselves. *The lack of such data will render any predictions about the effects of the formulations on glyphosate highly uncertain*.[299]

2. **Unknown Interactions:** Surfactants can be expected to interact with and perturb the structure, physical properties and function of membranes.[300]

3. **Objective Evidence is Lacking:** For specific mechanisms of interactions between glyphosate and surfactants.[301]

4. **Multiplicity of Potential Reactions:** The structural characteristics of extreme hydrophilicity and hydrophobicity of surfactants may result in very different interactions with hydrophobic and hydrophilic herbicides. Thus, the relatively water-soluble isopropylamine salt of glyphosate may interact differently with surfactants than the less water-soluble parent compound or other more insoluble herbicides.[302]

Indirect Disclosures of Surfactant and Co-Formulant Toxicity

In 2013, Mesnage, et al., published their study of nine herbicides containing glyphosate including five different formulations of Roundup. After studying the chemicals' patterns using mass spectrometry, Mesnage and his colleagues determined the identity of co-formulants in Roundup and performed toxicity analyses. They deduced the chemical structure of additives in six of the nine formulations and showed that each of these supposedly inert ingredients was more toxic than glyphosate alone.[303]

Subsequently, other studies have examined the toxicity of these co-formulants and measured significant enhancement of toxicity. While there occasionally may be performance differences between glyphosate products, these differences are more likely to be caused by the differences in surfactants formulated with the product.

Defarge, et al., 2016, study showed that each of the five co-formulants affected the function of both the mitochondria in human placental cells and aromatase, an enzyme that affects sexual development. Not only did these chemicals, which are not named on

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[299] Diamond, G., Durkin, P., "Effects of surfactants on the toxicity of glyphosate with specific reference to RODEO," 1997, Syracuse Research Corporation, SERA TR 97-206-1b.

[300] Id.

[301] Id.

[302] Id.

[303] Mesnage, R., Bernay, B., and Séralini, G.E., "Ethoxylated adjuvants of glyphosate-based herbicides are active principles of human cell toxicity," 2013, Toxicology 313(2-3), pp. 122-8.

herbicide labels, affect biological functions, they did so at levels far below the concentrations used in commercially available products. In fact, POEA, an "inert" ingredient, was between 1,200 and 2,000 times more toxic to cells than glyphosate, the "active" ingredient. They also reported that six glyphosate formulations similarly decreased aromatase activity in human placental cells at concentrations much lower than glyphosate alone. [304]

In a memorandum regarding risk assessment of "inert ingredients" in pesticide formulations, the U.S. EPA stated that although there are no dermal absorption data on the AAAPD and AAASD surfactants, the agency would expect the dermal absorption to be very low for these compounds. They base their conclusion on the physicochemical properties of these inert ingredients including their relatively high molecular weights and water solubility and on the fact that they are large, crosslinked molecules. This conclusion leads them to using 5% dermal absorption as a "likely upper bound, conservative value" in their risk assessment.[305]

The EPA also noted in this memorandum that there is no evidence that these surfactants are carcinogenic. This finding was based solely on a qualitative structural activity relationship (SAR) database (DEREK Version 11) which found no structural alerts. They also stated that there was little concern about any of the postulated metabolites having greater toxicity than the parent compounds.

Examples of Surfactant and Co-Formulant Toxicity

There is a general agreement and consensus that co-formulants can be more toxic for animals than glyphosate itself.[306] For example, cytotoxicity of the commercial formulation Roundup to human peripheral mononuclear cells was 30-fold higher (LC_{50} = 56 mg/L) than for the active ingredient (LC_{50}=1640 mg/L). Several *in vitro* and *in vivo*

[304] Defarge, N. et al., "Co-formulants in glyphosate-based herbicides disrupt aromatase activity in human cells below toxic levels," 2016, Int. J. Environ. Res. Public Health 13, p. 264.

[305] "Alkyl Alcohol Alkoxylate Phosphate and Sulfate derivatives (AAAPDs and AAASDs – JITF CST Inert Ingredients). Human health risk assessment to support proposed exemption from the requirement of a tolerance when used as inert ingredients in pesticide formulations." Memorandum from Office of Prevention, Pesticides, and Toxic Substances, US EPA, Washington, D.C. June 8, 2009.

[306] Defarge, N. et al., "Co-formulants in glyphosate-based herbicides disrupt aromatase activity in human cells below toxic levels," 2016, Int. J. Environ. Res. Public Health 13, p. 264.

studies with parallel testing of glyphosate active ingredient and Roundup showed that only the commercial formulation was genotoxic.[307]

New Zealand registration data revealed Roundup contained POEA.[308] Other formulations may contain much higher levels, even as high as 60-80% as in the Genamin formulation.[309] In studies using hepatic (HepG2), embryonic (HEK293) and placental (JEG3) cell lines to compare ten formulations of glyphosate, the most toxic were those that contained POEA. This surfactant induced necrosis and disrupted the structure and function of cell membranes with negative dose-dependent effects on cellular respiration and membrane integrity between 1 and 3 mg/L.[310]
POEA potentiates the effect of glyphosate facilitating its penetration of cell membranes and bioaccumulation in cells.[311] The bio-concentration factor for glyphosate is also increased in the presence of POEA in the aquatic environment.[312]

Endocrine Disrupting Effects of Glyphosate**

A review study by Ingaramo, et al., (2020)[313] summarizes current literature that has evaluated the endocrine-disrupting effect of glyphosate and glyphosate-based herbicides (GBHs) at low or environmentally-relevant doses in female reproductive tissues. Data suggests that at low doses, GBHs may have toxicologically adverse effects on the development of the female reproductive tract and fertility.

In the context of this study review, it is important to recognize that some formulas of GBHs contain surfactants which contain generally-recognized endocrine-disrupting chemicals (EDCs) at levels well above admissible levels in water. In vitro studies using human whole blood and estrogen-responsive cancer cell lines have found that exposure to GBHs induced proliferative effects and DNA damage with glyphosate impurities also contributing

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[307] Bolognesi, et al., “Biomonitoring of genotoxic risk in agricultural workers from five Colombian regions: Association to occupational exposure to glyphosate,” 2009, Journal of Toxicology and Environmental Health Part A, 72, pp. 986—997.

[308] Watts MA, “The poisoning of New Zealand,"1994, AIT Press, Auckland. From Pesticide Action Network (PAN). http://pan-international.org/wp-content/uploads/Glyphosate-monograph.pdf

[309] Mesnage, R. et al., “Ethoxylated adjuvants of glyphosate-based herbicides are active principles of human cell toxicity,” 2013.

[310] Id.

[311] Richard, S. et al., “Differential effects of glyphosate and Roundup on human placental cells and aromatase,” 2005, Environ Health Perspect 113(6), pp. 716-20.

[312] Annett R, Habibi HR, Hontela A., “Impact of glyphosate and glyphosate-based herbicides on the freshwater environment,” 2014, J Appl Toxicol 34(5), pp. 458-479.

[313] Ingaramo, P, et al., “Are glyphosate and glyphosate-based herbicides endocrine disruptors that alter female fertility?” 2020, Molecular and Cellular Endocrinology, 110934.

to toxicity. A genotoxicity study using HepG2 cells (best characterized human liver cell line used to study xenobiotic toxicity) found that, at sub-agricultural doses, anti-androgen effects and androgen to estrogen conversion by aromatase activity and mMRNA were disrupted with all formulations of glyphosate within 24 hours.

Li, et al., demonstrated that in human ovarian and prostate cancer cells, glyphosate and AMPA can inhibit proliferation and promote apoptosis. Animal cell studies have shown that glyphosate and/or GBHs may affect the female reproductive system via direct action on ovarian function. A recent study using breast cancer cell lines demonstrated that GBHs affects several pathways related to DNA damage repair, base excision repair, nucleotide excision repair and mismatch repair. In vivo fish studies have demonstrated a significant increase in the diameter of oocytes as well as developmental, reproductive and epigenetic effects.

Mammals are also susceptible. In female rats, sub-chronic doses of GBHs resulted in impaired folliculogenesis, altered ovary development, decreased estrogen secretion, oxidative stress and altered ovarian morphology suggesting that GBHs can induce endocrine-disrupting effects. Ewe lambs exposed to low doses of GBH from birth to postnatal day 15 demonstrated an increase in the number of atretic follicles and decrease in mRNA in both FSHR and growth/differentiation factor 9 suggestive of the promotion of growth arrest in developing follicles.

Previous studies have shown glyphosate and GBHs cause endocrine-disrupting effects on male reproduction at low doses. Both in vitro and in vivo studies have suggested that glyphosate and GBHs act on xenoestrogens through ERE activation. Animal models have demonstrated neonatal exposure to glyphosate and/or GBHs show altered ovarian and uterus development. These effects in turn can alter tissue morphology and function suggesting adverse effects on future fertility. Studies have shown glyphosate is able to cause endocrine disruption alone or in its formulations depending on dose, duration and frequency of exposure in males and females.

Endocrine disruption was also investigated by Munoz, et al., (2020)[314] who conducted a comprehensive review. The study produced important findings on glyphosate effects in the endocrine system and assessed mechanistic evidence to classify glyphosate as an EDC. Glyphosate has been shown via in vitro and in vivo studies to alter levels of estrogen

[314] Munoz, J.P., et al., "Glyphosate and the key characteristics of an endocrine disruptor: a review," 2020, Chemosphere.

receptor expression. There are also findings that glyphosate alters signaling pathways in hormone responsive cells. Even low concentrations of glyphosate can induce ER/ERK1/2 signaling pathways on ER positive cholangiocarcinoma cells altering expression levels of several proteins.

The study revealed that in breast cancer cell lines, exposure GBH with 1.1 mM glyphosate (0.05%) showed deregulation of eleven canonical pathways and induced expression of proliferative signaling-related proteins. There is evidence to suggest that glyphosate may be associated with epigenetic modifications in hormone-producing cells. These epigenetic changes were reported by direct exposure and through trans-generational assays.

Roundup® (but not pure glyphosate) has been found to alter biosynthesis of steroid hormone production. The mechanisms might be via effect on different proteins involved in biosynthesis including StAR, CYP aromatase and P450scc. GBHs have been shown in animal models to modify hormone concentration. Glyphosate exposure has shown direct effects on hormone-producing or hormone-responsive cells mainly on cell proliferation and apoptosis. Several animal models show that exposure to glyphosate or GBHs at different stages of development is associated with physiological changes including mammary gland, reproductive system and skeletal bone formation. These suggest an active role of glyphosate in altering hormone-producing cell fate.

Epidemiological evidence has shown that women exposed to glyphosate demonstrate an increased risk of late miscarriages and decrease in fecundability. Overall, mechanistic data showed that glyphosate exhibited eight of the ten key characteristics of an EDC: 1) can favor hormonal receptors activity, 2) disrupts levels of ER_{α} and ER_{β}, 3) induces deregulation of eleven canonical pathways in cancer breast cell lines, 4) induces epigenetic modifications in normal breast cell lines, 5) has adverse effects on steroid hormone production including estrogen and testosterone, 6) alters thyroid hormones transport across cell membrane, 7) modifies hormone concentration such as estrogen and testosterone in animal models, and 8) alters the proliferation rate of breast cell lines.

Regulatory Considerations Based on Surfactant and Co-Formulant Toxicity

In the absence of clear, unambiguous information pertaining to a commercial product's chemical composition, some countries take a hardline approach to regulation. For example, due to toxicity concerns, Germany removed glyphosate products containing

POEA from their market in 2014[315] and the European Union banned them in 2016.[316] The New Zealand Environmental Protection Agency (NZ EPA) has current approvals for 91 formulations of glyphosate of which 69 contain POEA. The New Zealand EPA refuses to name them "*because the composition of the formulations is commercial-in-confidence information.*"[317]

This situation is typical of many countries. The decree that banned the use of glyphosate formulations containing POEA in Italy named 55 formulations including well-known names such as Roundup, Rodeo® and Touchdown® and brands from Cheminova, Syngenta, Nufarm, Dow AgroSciences, and Arysta as well as Monsanto and some Italian companies.[318]

The key point here is that experimental studies suggest that the toxicity of POEA is greater than the toxicity of glyphosate alone and commercial formulations alone. However, safety evaluations performed by Monsanto have largely been performed on pure glyphosate or without identification of all ingredients. There is also evidence that glyphosate preparations containing POEA are more toxic than those containing alternative surfactants. Since surfactants contribute to the toxicity of glyphosate formulations, adverse health consequences are not necessarily caused by glyphosate alone but as a consequence of complex and variable mixtures. Even Monsanto has recognized this in correspondence (as cited in this assessment).

Monsanto TNO Dermal Penetration Study with Co-Formulant Cocoamine

Monsanto's previously reported dermal absorption studies did not include surfactant co-formulants. Monsanto did find evidence of the effects of one surfactant**,** cocoamine, on dermal absorption in their TNO dermal penetration studies. These studies were not submitted to the U.S. EPA or to any European regulatory agency.

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[315] Farrer P, & Falck M., "Toxic glyphosate herbicides fly under the EU's regulatory radar," 2014, Pesticides News 96, pp. 1-4.

[316] EC. 2016. Glyphosate. European Commission - Fact Sheet FAQs: Glyphosate. Brussels. June 29th. http://europa.eu/rapid/pressrelease_MEMO-16-2012_en.htm

[317] NZ Parliament. 2016. Written questions 10151, 10153, 10154. Steffan Browning to the Minister for the Environment. New Zealand Parliament Paremata Aotearoa, Wellington. https://www.parliament.nz/en/pb/order-paper-questions/written-questions/?criteria.Keyword=glyphosate

[318] Pesticide Action Network (PAN). http://pan-international.org/wp-content/uploads/Glyphosate-monograph.pdf

TNO Study: Johan van Burgsteden, "*In vitro* percutaneous absorption study with [14C]-glyphosate using viable rat skin membranes," June 14, 2002, Unaudited draft report V4478 (Tab 24).

Glyphosate in formulations MON 35012 and MON 0139 (70%) was examined for *in vitro* percutaneous absorption through viable rat skin membranes. Both contain the IPA salt of glyphosate, but MON 35012 also contains the surfactant cocoamine. Both the concentrated formulation and the field dilution were tested as shown in **Table 17**. After eight hours of exposure, the test substance was removed from the application site and samples of the receptor fluid were collected for an additional 40 hours.

Table 17
Formulations and Doses Tested in TNO Dermal Absorption Studies

Formulation	Ingredients	Dose (mg gly/cm^2)	
		Concentrate	Field dilution
MON 35012	Glyphosate Isopropylamine salt (46% w/w) Surfactant Cocoamine (18% w/w) Water & minor ingredients (35.5% w/w)	6.249	0.080
MON 0139 70%	Isopropylamine salt (62% w/w) Inert ingredients (38% w/w)	6.343	0.080

The investigators in this study used doses outside the range recommendations of the U.S. EPA's 1998 "Health Effects Test Guidelines" for dermal penetration as follows:

> The maximum practical dose is on the order of 1 mg/cm^2—larger doses tend to fall off the skin or exceed saturation of the absorption process. When only three doses are given, the highest dose should be on the order of 0.1 mg/cm^2.[319]

There are two doses in this study - the higher dose being 6.2 times larger than the recommended maximum dose. Furthermore, the U.S. EPA guidelines state that:

> The maximum dose volume should not exceed 10 µL/cm^2. Larger volumes of liquid have been found to flow on the skin and produce uneven distribution on the dosed area.[320]

[319] U.S. EPA OPPTS 870.7600, "Health Effects Test Guidelines Dermal Penetration," August 1998, p. 4.
[320] Id.

In this study, 10 µL of the test samples was applied on a 0.64 cm^2 skin surface area. This is the equivalent of 15.6 µL/cm^2 which is more than one- and one-half times greater than the recommended maximum (liquid) dose. The excess in both the concentration and the volume of the concentrated doses will contribute to absorption saturation as described by the U.S. EPA:

> The amount of chemical coverage on the skin surface can influence the amount of dermal absorption. Chemical coverage of the skin surface may be incomplete where only part of the surface is covered or it may be complete where the entire skin surface is covered. In both cases, only the amount of chemical in contact with the skin surface is available for absorption such that the capacity of the skin to absorb the chemical may be exceeded.[321]

The results of the eight-hour exposures are shown in **Table 18.**

Table 18

Percent Absorption of Glyphosate (percent of dose)

	MON 35012 (containing surfactant)		**MON 0319 (70%) (no surfactant)**	
	Penetration within 48 hrs	**Mass balance**	**Penetration within 48 hrs**	**Mass balance**
Dose	**% of dose**		**% of dose**	
Low dose	2.6 ± 1.4 % (2.10 µg/cm^2)	73.4 %	1.4 ± 2.2 % (1.13 µg/cm^2)	82 .6 %
High dose	10.3 ± 4.2 % (646.3 µg/cm^2)	132.4 %	1.3 ± 1.9 % (80.8 µg/cm^2)	128 .2 %

The following key points emerged from the exposure/absorption tests:

- The maximum penetration of **10.3 %** occurred with the higher dose of MON 35012 concentrate which contained the surfactant Cocoamine.
- Even at the lower glyphosate dose of 0.080 mg/cm^2 of MON 35012, the penetration was 2.6 % of the dose which is greater than Monsanto had previously reported.
- The mass balance was found to range from 73 % to 132 %. This variability is very high as guidelines cite an adequate mean recovery is in the range of 100 ± 10%. (OECD,

[321] U.S. EPA OPPTS 870.7600, "Health Effects Test Guidelines Dermal Penetration," August 1998, p. 3.

2004). This suggests variability in the amount of absorption among the rat skin membrane samples at each dosing.

- In fact, while the mean penetration of the higher dose in MON 35012 was 646.3 µg/cm^2, one membrane absorbed approximately 1,100 µg/cm^2, or about **18 %** of the applied dose. The mean penetration of the lower dose of MON 35012 was 2.10 µg/cm^2 while the maximum penetration was about 3.5 µg/cm^2 or approximately **4.4 %** of the applied dose.
- At the lower dose, using the worst-case scenario, the missing 27% of the dose should be included in the amount absorbed and, therefore, the amount of absorbed glyphosate would be 30% of the applied dose.

The measured 10.3 % dermal absorption of glyphosate through rat skin in the presence of a surfactant was not received well by Monsanto.

In a message from [redacted] (3-29-02) to [redacted] et al: Subject: "TNO dermal penetration studies: new issues and topics for the conference call of Tuesday, 2 April (8 A.M STL time)," the following was noted:

"As of today we received preliminary surprising results on *in vitro* dermal penetration of propachlor and glyphosate through rat skin; it is imperative that we work closely together and communicate well on the conduct, the practical difficulties and the results associated with these studies.

Glyphosate:

- The EU rapporteur for glyphosate used a dermal penetration factor of 3% based on several published *in vitro*/*in vivo* dermal penetration studies

- We launched human and rat *in vitro* dermal penetration studies with MON 35012 with and without surfactant

- Preliminary results with rat skin are not acceptable (see fax); due to very bad reproducibility (sic) that TNO cannot explain, they proposed to repeat the study in parallel with the human skin study. However, we can already conclude that:

a. For the concentrate MON 35012, the % *in vitro* dermal penetration of glyphosate through rat skin is between 5 and 10%

b. For the spray dilution of MON 35012, the % *in vitro* dermal penetration of glyphosate through rat skin will be around 2%

c. The dermal penetration of glyphosate itself in the absence of surfactant is lower than 1.5%."

A follow-up communication from Mr. William Heydens (4-2-02, to Charles Healy): Subject: "TNO dermal penetration studies: new issues and topics for the conf call of Tuesday, 2 April (8 A.M STL time)."

> "… My primary concern is with the glyphosate in terms of the potential for this work to blow Roundup risk evaluations (getting a much higher dermal penetration than we've ever seen before)."

Monsanto did not share this study with the public or the scientific community. Additionally, Monsanto decided not to have it repeated. Some incidental communications on this subject are available for consideration:

[redacted] (4-4-02):

> "Although we agreed to repeat the *in vitro* dermal penetration study with rat skins as proposed by TNO, we came to the conclusion that the penetration of glyphosate would have been [probably] greater than the 3% already imposed by the German authorities. We decided thus to STOP the study (effective today morning)."

With further explanation, [redacted] (4-5-02):

> "…we initiated the studies from a regulatory angle to help meet the requirements for operator exposure, given that the Annex I endpoint for dermal absorption for glyphosate was set at 3%, …the results of the rat skin studies show levels of absorption for glyphosate of a similar order to the Annex I endpoint; also confirm our expectation that surfactant concentration affects the dermal absorption… therefore, from the regulatory angle, there is no point in pursuing the studies further."

Humectants

In addition to surfactants, Roundup formulations also contain humectants which reduce the loss of moisture. As Monsanto notes,[322]

> "**Certain co-formulants like humectants that will make it highly likely we will get large amounts penetrating the skin."**

Humectants include chemicals such as ethylene glycol (anti-freeze). Ethylene glycol is included in most Roundup formulations. In addition to increasing dermal absorption,

[322] MONGLY06653096.

ethylene glycol is a toxic chemical in and of itself.[323] It is uncertain whether Monsanto ever studied the effect of ethylene glycol on glyphosate dermal absorption.[324]

Adjuvants

Adjuvants may be added to glyphosate formulations prior to use to improve their efficacy against weeds by enhancing penetration of glyphosate into the target plant. However, many of these may also increase the toxicity of glyphosate to other species. For example, organosilicone surfactants, described as the most potent of adjuvants and commonly added to glyphosate formulations, are now linked to a decline in honeybees in the U.S.[325] The common adjuvant surfactant TN-20 used in glyphosate formulations caused cell death and mitochondrial damage in rat cells which disrupts the integrity of the cellular barrier to glyphosate and promotes its toxicity.[326] Martini, et al., (2016) demonstrated that adjuvants other than POEA inhibited proliferation and differentiation of mammalian 3T3-L1 fibroblasts to adipocytes.[327]

Enhanced Absorption Due to Skin Damage

Skin, by its nature, is often compromised due to cracking and fissures, by cuts, scrapes, chemical damage, water-submersion, burns, sensitivity reactions, eczema and infections. This is particularly true for outdoor workers. Breaks in the protective lipophilic barrier of the stratum corneum significantly increase absorption of hydrophilic compounds. A compromised protective lipid barrier will allow the hydrophilic glyphosate to pass through into the hydrophilic dermis, thus avoiding slow diffusion through the lipid layer. Percutaneous absorption studies have demonstrated that glyphosate deposition in damaged skin is five times that of healthy skin and penetration through damaged skin is increased 20-fold.[328] The integrity of the skin also effects the distribution of chemicals

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[323] MONGLY01832749. (Toxic to children at 70 cc of Roundup with 5% ethylene glycol.)

[324] MONGLY01745304.

[325] Mullin CA, Fine JD, Reynolds RD, Frazier MT, "Toxicological risks of agrochemical spray adjuvants: organosilicone surfactants may not be safe," 2016, Front Public Health, 4:92.

[326] Kim YH, Hong JR, Gil HW, Song HY, Hong SY, "Mixtures of glyphosate and surfactant TN20 accelerate cell death via mitochondrial damage-induced apoptosis and necrosis," 2013, Toxicol *In Vitro* 27(1), pp.191-197.

[327] Martini, C. et al., "Glyphosate-based herbicides with different adjuvants are more potent inhibitors of 3T3-L1 fibroblast proliferation and differentiation to adipocytes than glyphosate alone," 2016, Comparative Clinical Pathology, Volume 25, Issue 3, pp. 607–613.

[328] Nielsen, J. et al., "Defense against dermal exposures is only skin deep: significantly increased penetration through slightly damaged skin," 2007, Arch Dermatol Res, Vol. 299, pp. 423-431.

within the skin compartments which will have implications in the efficacy of hand-washing after herbicide exposure.[329]

With respect to applicators, the acute quantity of glyphosate entering the skin is low. However, with repeated doses, especially coupled with a failure to wash the skin before it can be absorbed, the cumulative dose increases. Studies have documented that glyphosate penetration of skin increases linearly with time. Thus, if the worker is unaware of the exposures, absorption continues.[330]

Glyphosate's Role in Skin Damage

Evidence of glyphosate interference with mitochondrial function is increasingly emerging in the scientific literature. Mitochondria are the powerhouse bodies within cells which are necessary in the programmed cell death needed to form skin. Impairment of mitochondrial function reduces the transition of dermal to epidermal cells leading to a decrease in the protective epidermis.[331]

Additional studies by Heu, et al., have demonstrated glyphosate-induced structural changes.[332] In these studies, the control cells show Young's modulus values respectively increasing approximately 4-fold for 6 hours and 3-fold for 18 hours. These increases reflect a significant rise in cell stiffness. Heu, et al., reported that after a gentle cytotoxic treatment (6 h, 15 mm-glyphosate), the topography profile changes. The cells exhibit a flattened membrane and a different distribution of native protrusions. They also show a complex subcellular filamentous network with numerous membrane junction points.[333] Thus, glyphosate itself has an intrinsic propensity to damage skin.

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[329] Id.

[330] Kezic, S. & Nielsen, J.B, "Absorption of chemicals through compromised skin," 2009, International Archives of Occupational and Environmental Health, Vol. 82(6), pp. 677-88.

[331] Heu, C., et al., "A step further toward glyphosate-induced epidermal cell death: Involvement of mitochondrial and oxidative mechanisms," 2012, Environmental Toxicology and Pharmacology 34.

[332] Heu C, Berquand A, Elie-Caille C, Nicod L., "Glyphosate induced stiffening of HaCat keratinocytes, a Peak Force Tapping study in living cells," 2012, J Struc Biol 178, pp. 1-7.

[333] Id.

Other Factors Increasing Dermal Absorption

Various skin cream compounds applied to the skin prior to handling pesticides have been demonstrated to alter percutaneous absorption as reported in a study by Brand, et al., (2007).[334] In these studies, four commercially available moisturizing creams were tested with respect to their capacity as transdermal penetration enhancers using the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) as a model compound. Their data demonstrated that pre-treatment with three of the four creams increased the absorption of 2,4-D as evidenced by either an increased cumulative penetration or shorter lag-times.

Korinth, et al., (2003) reported that skin barrier creams have been demonstrated to enhance the penetration rates of different industrial solvents. The creams significantly enhanced the penetration rates of solvents from complex mixtures compared with the single solvents.[335]

Water-in-oil emulsions, such as oily creams, retard water loss from the skin thereby increasing hydration but also increasing the permeability of the skin.[336] Oil-in-water emulsions (water-based creams) may donate water to the skin thereby increasing hydration and also slightly increasing the skin's permeability.[337]

Wester and Maibach (2015)[338] reported on the absorption of a 1% glyphosate solution from cotton cloth into and through human skin. Cotton cloth was dosed with a 1% glyphosate solution and applied to the skin. It was found that 0.7 ± 0.3 % was absorbed compared to 1.4 ± 0.2 % dose absorbed when the solution was dosed directly on the skin. Allowing the cotton cloth to air dry for one day further reduced the absorption to 0.08 ± 0.01 %.

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[334] Brand, R. et al., "Transdermal absorption of the herbicide 2,4-dichlorophenoxyacetic acid is enhanced by both ethanol consumption and sunscreen application," 2007, Food and Chemical Toxicology, Volume 45, Issue 1, pp. 93-97.

[335] Korinth G, Geh S, Schaller KH, Drexler H., "*In vitro* evaluation of the efficacy of skin barrier creams and protective gloves on percutaneous absorption of industrial solvents," 2003, Int Arch Occup Environ Health, Vol. 76(5), pp. 382-6.

[336] Smith, Eric and Maibach, Howard, eds., Percutaneous Penetration Enhancers (Boca Raton, FL: CRC Press, 2015.

[337] Id.

[338] Wester, R. and Maibach, H. (2015). 'Penetration enhancement by Skin Hydration', in Smith, E. and Maibach, H. (eds.) Percutaneous Penetration Enhancers (Boca Raton, FL) CRC Press, 2015.

However, after adding water to the dried cotton-glyphosate cloth, the absorption increased to 0.4 ± 0.1 % indicating that water "activated" the glyphosate. The water was acting as an external solvent and as such, increased the percutaneous absorption.

Ethanol is also well known as a topical penetration enhancer as it is frequently used in transdermal drug delivery systems (patches). Bommannan, et al., (1991)[339] found that, during *in vivo* studies with human skin, ethanol enters the skin and removes measurable quantities of the lipid barrier material from the stratum corneum. This lipid extraction may lower the skin barrier function and render the membrane more permeable which is the most likely explanation for the effect of ethanol as a skin penetration enhancer.

The mechanism by which ethanol facilitates permeation of a solute, such as glyphosate, is referred to as the "'pull" (or "drag") effect.[340] Hand sanitizer use has become widespread in the U.S. and typical hand sanitizers contain on average of 62% ethanol.

Thus, the use of creams and lotions to treat dry, cracking skin as well as the use of hand sanitizers potentiate the dermal absorption of glyphosate among occupational applicators.

[339] Bommannan D, Potts RO, Guy RH, "Examination of the effect of ethanol on human stratum-corneum *in vivo* using infrared-spectroscopy," 1991, J Control Release, Vol. 16, pp. 299–304.

[340] Heard CM, Kung D, Thomas CP, "Skin penetration enhancement of mefenamic acid by ethanol and 1,8-cineole can be explained by the "pull" effect," 2006, Int J Pharm., Vol. 321, pp. 167–170.

4. Toxicological Assessment of Glyphosate Exposures

(Systemic Exposure & Mechanism of NHL Induction)

Non-Hodgkin's Lymphoma Latency Estimates

The term "latency" refers to the interval between initial exposure to a cancer-causing chemical and when a physician initially diagnoses the cancer on the basis of objective clinical evidence.

A chemical's genotoxicity may lead to cancer-inducing mutations in cells; however, a distinct amount of time elapses during which mutations and DNA damage accumulate in cells before cancer becomes clinically evident. Additionally, a sufficient number of doubling times are required. Latency refers to the time between initial exposure to a cancer-causing chemical and when a physician initially diagnoses the cancer.

There is no single peer-reviewed, generally-recognized latency "threshold" for the more than 60 subtypes of lymphoma (Morton, et al., 2014).[341] Various sources cite latency intervals ranging as high as 25 years or more. Most estimates are based upon absence of information as opposed to hard evidence.

From the compilation of peer-reviewed latency estimates in **Table 19**, a surmised latency interval of 2 to 25 years falls within the general estimates of the studies cited therein. Although no single study is conclusive and future studies will undoubtedly clarify this issue, the current weight of study evidence suggests that this range offers an acceptable degree of objective scientific evidence.

[341] Morton, et al., "Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the Inter-Lymph Non-Hodgkin Lymphoma Subtypes Project," August 2014, J Natl Cancer Inst Monogr. (48), pp. 130-44.

Table 19
Compilation of Peer-Reviewed NHL Latency Estimates

Study/Source	Summary of Findings	Latency
USEPA Glyphosate Issue Paper: 57, 2016[342]	"Some have argued that the follow-up period (median=7 years) De Roos, et al. (2005) is not sufficiently long to account for the latency of NHL (Portier, et al., 2016); however, the latency period for NHL following environmental exposures is relatively unknown and estimates have ranged from 1-25 years (Fontana et al., 1998; Kato et al., 2005; Weisenburger, 1992)." *All of the preceding references are in USEPA Glyphosate Issue Paper as cited*.	1 to 25 yrs.
USEPA Glyphosate Issue Paper: Sept. 2016	"Eriksson, et al., (2008) evaluated the impact of time since first exposure. This study found an increased effect estimate for subjects with more than 10 years of glyphosate exposure prior to diagnosis of NHL. This finding suggests a potential for a longer latency for NHL than the follow-up period in De Roos, et al. (2005)." *All of the preceding references are in USEPA Glyphosate Issue Paper as cited*.	10 yrs.
USEPA Glyphosate Issue Paper: September, 2016	"Two case-control studies evaluating the risk of NHL (Eriksson, et al., 2008 and McDuffie, et al., 2001) observed increased effect estimates in the highest exposure categories analyzed. Eriksson, et al. (2008) found a greater effect estimate for subjects with >10 days (based on the median days of exposure among controls) and >10 years of exposure (for latency analysis) when compared to subjects with = 10 days and 1-10 years of exposure, respectively; … however, given the latency analysis of NHL was limited to Eriksson, et al. (2008) and lack of NHL latency understanding in general, further studies are needed to determine the true latency of NHL. McDuffie, et al. (2001), stratifying based on the average number of days per year of exposure, observed similar effect estimates in the lower exposure category (>0 and = 2 days/year) while a greater effect estimate was observed in the highest exposure category (>2 days/year)."	10 yrs.
9-11 Monitoring and Treatment, World Trade Center Health Program[343]	"The reported minimum latency estimate using statistical modeling in epidemiologic studies for … lymphoproliferative and hematopoietic malignancies resulting from formaldehyde exposure is 2 years [Latency Method 4A] (Beane Freeman et al. 2009)." "A minimum latency period of 2 years has been reported for non-Hodgkin lymphoma (Bennett, et al. 1991) following treatment of Hodgkin disease with chemotherapy and radiotherapy which is similar to the latency for secondary acute leukemia (Nadler and Zurbenko 2013; Tucker et al. 1988)." *All of the preceding references are in 9-11 Monitoring report as cited*.	2 yrs. (min)

[342] USEPA, "Glyphosate Issue Paper: Evaluation of Carcinogenic Potential," USEPA's Office of Pesticide Programs, September 12, 2016, https://www.epa.gov/sites/production/files/2016-09/documents/glyphosate_issue_paper_evaluation_of_carcincogenic_potential.pdf

[343] "Minimum Latency & Types or Categories of Cancer," World Trade Center Health Program, Revised: January 6, 2015, https://www.cdc.gov/wtc/pdfs/policies/WTCHP-Minimum-Cancer-Latency-PP-01062015-508.pdf

Additional NHL Risk Factors**

An objective toxicological assessment requires review of both known and potential risk factors. Exposure circumstances thus play key roles in the toxicological investigation. For example, if exposure to a certain substance is generally recognized to increase the individual risk for diagnosis of a clinical condition (such as NHL), then exposure becomes the *primary line of toxicological inquiry*. Exploration of exposure circumstances inevitably leads to frequencies, durations and dose(s).

In the present matter, other substances are potentially capable of inducing some of the toxicological effects noted. The following sections review several of these substances.

Benzene as Potential NHL Risk Factor**

The U.S. EPA has classified benzene as a known human carcinogen for all routes of exposure.[344] Studies gauge benzene exposure on the basis of dose per interval at a given air level; in this case, ppm per year ("ppm-years"). For example, an exposure of 1 ppm of benzene for 40 years results in 40 ppm-years duration of exposure.

Khalade, et al., (2010) conducted a meta-analysis to determine the relationship between benzene exposure and cancer risk (effect size). Summary effect size estimate for any leukemia was 1.64, 1.90 and 2.62, respectively, for low (> 0, < 40 ppm-years), medium (40-99.9 ppm-years) and high (> 100 ppm-years) exposures. The risk of acute myeloid leukemia (AML) was estimated to be 2-fold for cumulative exposure below 40 ppm-years, 2.3-fold for exposure from 40 ppm-years to below 100 ppm-years, and over 3-fold for exposures 100 ppm-years and above. A significant risk for developing AML from benzene exposure occurs by excessive cumulative exposure of greater than 250 ppm-years or a peak benzene exposure of 20 ppm.

While a high and significant risk of AML has been widely reported across studies, results on chronic lymphocytic leukemia (CLL, a subtype of NHL) remain controversial. In this analysis, the highest exposure category for CLL was based on only one study. Additionally, there was a lack of consistent association between benzene exposure and risk of chronic myelogenous leukemia (CML) and insufficient evidence to make any inference on effects to acute lymphoblastic leukemia (ALL).

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[344] "Benzene: Hazard Summary," U.S. EPA, January 2012, https://www.epa.gov/sites/production/files/2016-09/documents/benzene.pdf

A study by Khalade, A., et al, demonstrated that occupational benzene exposure increases the risk of leukemia in a dose-response pattern.[345] Cumulative benzene exposures at greater than 40 ppm-years begin to significantly increase the risk for leukemia. Outside of the occupational setting, a substantial amount of benzene exposure over a long period of time would have to occur. As previously noted, exposure circumstances are toxicologically critical in assessing dose. Pumping gas into a vehicle, for example, does not produce a high enough dose of benzene exposure to significantly increase the risk of leukemia.

[345] Khalade, A., et al., "Exposure to benzene at work and the risk of leukemia: a systematic review and meta-analysis," 2010, Environmental Health, Vol. 9(31).

Smoking as Potential NHL Risk Factor**

Morton, et al., (2003)[346] conducted a study among women to evaluate smoking as an NHL risk factor. The results suggested that smoking does not alter the risk of all NHL subtypes combined but strongly demonstrated an increased risk of follicular lymphoma. This appears to be associated with increased intensity and duration of smoking and cumulative lifetime exposure to smoking. Compared with nonsmokers, women with a cumulative lifetime exposure of 16-33 pack-years and 34 pack-years or greater experienced a 50% increased risk (OR=1.5, 95% CI 0.9-2.5) and 80% increased risk (OR=1.8, 95% CI 1.1-3.2), respectively, of follicular lymphoma (*P* for linear trend= 0.05).

Similarly, studies by Herrinton, et al., (1998)[347] observed a positive association between smoking and the risk of follicular lymphoma as compared with nonsmokers (former smokers, relative risk=1.9, 95% CI 1.2-2.9; current smokers, relative risk=1.4, 95% CI 0.9-2.2). The strength of association did not increase consistently with increasing duration and intensity of smoking. The authors observed no relationship between smoking status and risks of small cell lymphocytic, diffuse or high-grade lymphoma nor was smoking related to the risk of all histological types of NHL combined. The results give limited evidence for a relationship between smoking and risk of follicular lymphoma.

Bracci, et al., (2005)[348] conducted a population-based, case-control study of NHL and tobacco use. For men, an increased risk for follicular lymphoma was observed for cigarette smokers and other tobacco (OR=1.5, 95% CI 1.0-2.2), cigars alone (OR=2.8, 95% CI 1.1-7.2) and snuff or chewing tobacco alone (OR=7.3, 95% CI 1.9-28) while there was no association with tobacco use and follicular lymphoma among women. The results did not support an association between overall tobacco use and all NHL in men or women. Risk estimates for follicular lymphoma in men related to smoking characteristics were increased but not linear and not different from unity.

A single study found a nearly 4-fold increased OR for diffuse large-cell lymphoma associated with use of non-cigarette tobacco in men only (OR=3.9, 95% CI 1.6-9.6). ORs

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[346] Morton, LM., et al., “Cigarette smoking and risk of non-Hodgkin’s lymphoma subtypes among women,” British Journal of Cancer, Vol. 28, pp. 2087-2092.

[347] Herrinton, LJ, et al., “Cigarette smoking and risk of non-Hodgkin’s lymphoma subtypes,” January 1998, Cancer Epidemiology, Biomarkers & Prevention, Vol. 7, pp 25-28.

[348] Bracci, P.M. & Holly, E.A., “Tobacco use and non-Hodgkin lymphoma: results from a population-based case-control study in San Francisco Bay Area, California,” 2005, Cancer Causes and Control, Vol. 16, pp. 333-346.

were increased for NHL among men who used any non-cigarette tobacco alone (OR=1.7), non-cigarette tobacco and cigarettes (OR=1.4).

Besson, et al., (2003)[349] conducted a hospital-based, case-control study to determine the relationship between smoking and NHL. The results of this study suggested a 3-fold increase in the risk of follicular NHL among current smokers (OR=3.20, 95% CI 0.79-12.97) but the result was not statistically significant, perhaps due to small sample size. Risk of NHL was more than 2-fold higher for women who currently smoke compared to women who have never smoked (OR=2.40, 95% CI 1.19-4.84). Among ever smokers, a significant increased risk of NHL was observed for women who have smoked for more than 30 years compared with women who have never smoked (OR=5.04, 95%CI 1.40-18.12). There was an association between smoking duration and follicular lymphoma although a smaller number limited the ability to find a statistical significance.

Parker, et al., (2000)[350] conducted a population-based cohort study of older women (aged 55-69) and observed an increased risk with smoking and follicular lymphoma in former and current smokers after multivariate adjustment (RR=1.6, 95% CI 0.7-3.4 and RR=2.3, 95% CI 1.0-5.0, respectively) as compared to never smokers. After multivariate adjustment, current smokers had a significant increased risk of developing follicular lymphoma compared to never smokers.

Taborelli, et al., (2017)[351] conducted a hospital-based, case-control study to determine the relationship between tobacco smoking and risk of NHL and Hodgkin lymphoma (HL) through logistic regression spline models. Regarding significant increased risks of both NHL and HL in smokers (≥ 15 cigarettes/day) compared to never smokers; the risk was more elevated for follicular lymphoma (OR=2.43, 95% CI 1.31-4.51). The Taborelli study, "Table 3," (see **Figure 17**) shows the results for risk of NHL subtypes and smoking highlighting follicular lymphoma. No excess risk was observed for former smokers or people smoking <15 cigarettes/day. This study demonstrated a positive dose response relationship with significant increases in NHL starting from 15 cigarettes/day with more evident effects for follicular lymphoma starting from 7 cigarettes/day.

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[349] Besson, H., et al., "Smoking and non-Hodgkin's lymphoma- a case control study in the Rhone-Alpes region of France," 2003, Cancer Causes Control, Vol. 14(4), pp. 381-398.

[350] Parker, A.S., et al., "Smoking and Risk of Non-Hodgkin Lymphoma Subtypes in a Cohort of Older Women," 2000, Leukemia and Lymphoma, Vol. 37(3-4), pp. 341-349.

[351] Taborelli, M., et al., "The dose-response relationship between tobacco smoking and the risk of lymphomas: a case-control study," 2017, BMC Cancer, Vol. 17:421.

Table 3 Risk of non-Hodgkin and Hodgkin lymphoma subtypes according to smoking habits

	Smoking habits[a]					
	Never[b]	Current				
		<15 cig/day		≥15 cig/day		χ^2 for trend
	No.	No.	OR (95% CI)	No.	OR (95% CI)	
Non-Hodgkin lymphoma						
Mature B-cell lymphomas	219	67	0.95 (0.67–1.34)	95	1.37 (0.97–1.92)	$p = 0.09$
DLBCL	133	33	0.76 (0.49–1.18)	49	1.09 (0.72–1.66)	$p = 0.88$
Burkitt	5	4	3.07 (0.74–12.81)	4	3.30 (0.71–15.28)	$p = 0.16$
Follicular	39	18	1.31 (0.69–2.47)	25	2.43 (1.31–4.51)	$p < 0.01$
Mantle cell	4	1	0.66 (0.07–6.41)	2	1.04 (0.17–6.50)	$p = 0.99$
Marginal zone	16	3	0.66 (0.18–2.44)	4	1.09 (0.33–3.66)	$p = 0.80$
Lymphoplasmacytic	8	3	1.56 (0.38–6.48)	2	0.87 (0.16–4.86)	$p = 0.99$
SLL/CLL	8	4	1.41 (0.40–4.93)	7	2.47 (0.81–7.59)	$p = 0.06$
Other B-cell lymphomas	6	1	0.45 (0.05–4.15)	2	2.87 (0.41–20.02)	$p = 0.46$
Mature T-cell lymphomas	14	8	1.83 (0.72–4.62)	6	1.72 (0.59–5.03)	$p = 0.15$
Other or NOS	6	3	1.20 (0.75–1.91)	7	2.30 (1.40–3.77)	$p < 0.01$
Hodgkin lymphoma						
Nodular sclerosis	61	28	1.14 (0.61–2.12)	18	1.76 (0.78–3.98)	$p = 0.23$
Mixed cellularity	6	2	1.02 (0.16–6.66)	10	5.60 (1.31–23.97)	$p = 0.03$
Other or NOS	18	6	0.78 (0.27–2.21)	15	3.22 (1.15–9.04)	$p = 0.06$

Odds ratios (OR) and 95% confidence intervals (CI) were estimated using unconditional logistic regression model adjusted for gender, age, study center, years of education, and place of birth

CLL Chronic lymphocytic leukemia, *DLBCL* Diffuse large B-cell lymphoma, *NOS* Not otherwise specified, *SLL* Small lymphocytic lymphoma

[a]Former smokers excluded. [b]Reference category

Figure 17: "Table 3" from Taborelli, et al., study results as published (2017) [352]

Overall, the human epidemiological studies are consistent with a positive association of smoking tobacco and the risk of follicular NHL. Cumulative lifetime exposures of 16-33 pack/years in women smokers have shown a 50% increased risk for follicular lymphoma. Of significance, cessation of smoking (former smokers) reduces the risk of NHL to baseline.

[352] Id.

Obesity and BMI as Potential NHL Risk Factors**

Larsson & Wolk (2011)[353] conducted a meta-analysis investigating the relationship between body mass index (BMI) and NHL (and subtype) incidence and mortality.

A slight increased risk (7%) of NHL was observed with a 5 kg/m^2 increment in BMI (RR= 1.07, 85% CI 1.04-1.10) over 16 studies. The relative risk of NHL mortality associated with a 5 kg/m^2 increase in BMI was 1.14 (95% CI, 1.04-1.26) over five studies; however, there was also notable diversity (e.g., heterogeneity) among studies.

There were no statistically-significant positive associations of BMI with risk of subtypes of NHL except for diffuse large B-cell (RR=1.13, 95% CI 1.02-1.26). There was only a small increase in risk of NHL associated with excess body weight which is very low compared to more than a 2-fold risk of NHL as a consequence of glyphosate exposure.

The study findings demonstrate BMI to be a low but measurable risk consideration with respect to NHL and excess weight in the obese range. The findings also suggest slightly increased NHL risk among high-BMI women versus men.

[353] Larsson, S.C. & Wolk, A., "Body mass index and risk of non-Hodgkin's and Hodgkin's lymphoma: A meta-analysis of prospective studies," 2011, European Journal of Cancer, Vol. 47, pp. 2422-2430.

Carcinogenicity of Other Herbicides & Pesticides According to Monsanto**

On June 17, 2019, in the matter of Adams v. Monsanto, the company submitted an *"Amended Responses to Plaintiff's First Set of Requests for Admission."* This 70 page document presents a series of formal denials regarding carcinogenicity of Monsanto's non-glyphosate herbicides and pesticides. Applicable substances noted therein include 2,4-D, alachlor, atrazine, carbaryl and DDT as follows:

- Monsanto denies that 2,4-D is carcinogenic.[354] Monsanto states, *"the scientific evidence does not demonstrate that 2,4-D is carcinogenic in humans."*[355]
- Monsanto denies that alachlor is carcinogenic. Monsanto states, *"the scientific evidence does not demonstrate that alachlor is carcinogenic in humans."*[356]
- Monsanto denies that atrazine is carcinogenic. Monsanto states, *"the scientific evidence does not demonstrate that atrazine is carcinogenic in humans."*[357]
- Monsanto objects to the request to admit that the commercial carbaryl formulations are carcinogenic as this calls for an expert opinion which is "not a proper inquiry" for the Request for Admission.[358] Monsanto states, *"it does not have requisite scientific knowledge to affirm or deny that carbaryl is carcinogenic in humans."*[359]
- Monsanto objects to the request to admit that commercial DDT formulations are carcinogenic as this calls for an expert opinion which is "not a proper inquiry" for the Request for Admission.[360] Monsanto states, *"it does not have requisite scientific knowledge to affirm or deny that DDT is carcinogenic to humans."*[361]

[354] Monsanto Company's Amended Responses to Plaintiff's First Set of Requests for Admission (Adams, James, et al., v Monsanto)

[355] Monsanto Company's Amended Responses to Plaintiff's First Set of Requests for Admission, James Adams, et al., Plaintiffs, v. Monsanto Company, Defendant., Case No. 17SL-CC02721, pp. 4-5, 9/65.

[356] Id., p. 19/65.

[357] Id., p. 22/65.

[358] Id., p. 33/65.

[359] Id., pp. 32-33/65.

[360] Id., p. 43/65.

[361] Id., p. 43/65.

Summary of Objective Toxicological Factors

The generally-accepted, peer-reviewed toxicological literature is not based on unsubstantiated, subjective opinions, but rather statistically significant data at the 95% level of confidence. The various 8 prongs of the well-established Braford Hill criteria have been evaluated in my assessment by considering the strength of various associations within genotoxicity and other mechanistic studies, the specificity of the adverse effect(s) as well as their consistencies among different studies.

Additionally, dose-responsiveness has been evaluated among the various genotoxicity and other mechanistic studies as referenced within this report (in some cases using human equivalent dosing (HED methodology). Also, coherence of studies among different study designs has been considered along with latency (temporality) and experimental studies in which animal dose equivalency comparisons to human dosage were assessed.

Expert opinions must always be based on objective, reliable evidence without deviation from the generally accepted methodology. Using the weight-of-evidence methodology of significant findings within the human epidemiological studies that employ dose-metrics, coupled with a scientific understanding of the genotoxic mechanisms, bone distribution/ADME and the mechanisms in which the Roundup mixtures are absorbed, distributed to bone marrow and other locations, retention time in such tissues prior to metabolism and excretion, reliable toxicological opinions are provided.

The evidence of glyphosate potency when applied as a chemical mixture has also been evaluated from both mechanistic findings and dose-response evidence. Mr. Cervantes' exposure histories have been compared to the dose-metrics in human epidemiological studies with respect to determining whether 8-hour time-weighted exposure day thresholds were exceeded.

Evidential Considerations

The following evidential factors are useful in formulating an objective toxicological assessment of Mr. Cervantes with regard to his Roundup® exposures and subsequent NHL diagnosis:

- **Diagnosis:** Mr. Cervantes' pathology report provides a diagnosis of diffuse large B-cell lymphoma (non-Hodgkin's lymphoma) which was at "Stage IV" upon detection and diagnosis. The cancer was successfully put into remission by his first round of treatment. However, after several years of comparative good health, Mr. Cervantes again began experiencing night sweats, fatigue, bone and joint aches and other symptoms. A second round of aggressive treatment was applied (successful to date).
- **Prolonged Acute Exposure and Absorption**: Mr. Cervantes testified that he regularly contacted Roundup® on his skin. He never wore a mask or other personal protective equipment while using Roundup®. He used concentrated Roundup® which he mixed in a 3 gallon sprayer. He wore only absorbent gloves and leather boots when mixing and applying Roundup.® His deposition testimony and interview reveal a quantifiable pattern of exposure indicative of episodic, prolonged, acute dermal exposure and absorption over a period of approximately 22 years.
- **Chronic Glyphosate Exposure:** Mr. Cervantes used almost no personal protective equipment (PPE) as a matter of standard procedure. He noted in deposition and in interview that he experienced direct dermal exposure to liquid Roundup® as he wore only absorbent clothing and cotton gloves (sometimes no gloves at all). He occasionally got Roundup® on his hands and would sometimes rinse, but only if possible and/or practical; otherwise, he would merely wipe off the concentrate solution and continue on to the next task.[362] Frequency of liquid contact with forearms, hands, legs and feet are all important toxicological considerations. Additionally, the time between exposure and bathing with soap is important with respect to continued absorption especially if the applicator wore Roundup-contaminated clothing for extended periods as acute exposure doses periodically left on the skin for prolonged periods further enhance dermal absorption.
- **Dermal Absorption Rates Higher than Presented by Monsanto**: As previously discussed in great detail, the correct dermal absorption rate for glyphosate ranges between 3% and greater (as opposed to the defective values recently issued by Monsanto's contractor, DTL Laboratory). Additionally, numerous other factors are

[362] Deposition of Gerard F. Cervantes, June 23, 2020, pp. 142-143.

known to increase skin absorption of glyphosate including (but not limited to) elevated temperatures, continuing to wear herbicide-soaked clothing and gloves, sweating (which contributes to increased skin absorption) and cracked skin as well as the various surfactants formulated in the actual Roundup products (as most of the dermal absorption studies were performed on pure glyphosate without the additives).

Lack of Personal Protective Equipment (PPE): Mr. Cervantes was not instructed via the product label to wear personal protective equipment such as impermeable pants, boots, mask, long sleeve shirt, face shield, *chemically-resistant* gloves, etc. He believed Roundup® was "safe" to use for many reasons and proceeded accordingly. Notably, Monsanto employees (in the previously referenced study) were protected with PPE on all exposed body areas during their own dermal exposure testing procedures, but consumers are not protected because the product label provides no such instructions.[363] (Even though the Monsanto research study and report recommended multiple warnings with respect to PPE.)

- **Mechanism of Carcinogenicity:** Mr. Cervantes' exposures are to Roundup® product, not to glyphosate alone. Roundup® and glyphosate have been demonstrated in several studies to repeatedly cause DNA damage with promotion by Roundup® being more damaging than glyphosate alone. Genotoxicity is the first stage in cancer formation. Wozniak, et al.,[364] and other studies as referenced in this report further demonstrated that Roundup®, at a higher dose, was even able to impede the natural repair of damaged DNA.

  The George, et al., study[365] documented cancer promotion at relatively low dermal exposure doses in mice. The dose levels, when converted to human doses, are reasonably similar to that sustained by applicators (when applying the HED factor and dermal absorption rate of 3%). More importantly, the test model employed DMBA (as found in cigarette smoke/tar). This primary carcinogen was dermally applied at low doses on the shaved skin of mice with no tumors produced unless glyphosate was also applied to the skin in which case 40% of the animals developed tumors (2.8 tumors per animal). The mechanism of glyphosate carcinogenesis is important with respect to tumor promotion among smokers prior to the onset of NHL. The George

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[363] Some later labels included recommendation of gloves during mixing.

[364] Wozniak, E., et al., "The mechanism of DNA damage induced by Roundup 360 PLUS, glyphosate and AMPA in human peripheral blood mononuclear cells – genotoxic risk assessment," 2018, Food and Chemical Toxicology, doi: 10.1016/j.fct.2018.07.035

[365] George, J., et al., "Studies on glyphosate-induced carcinogenicity in mouse skin: A proteomic approach," 2010, Journal of Proteomics, Vol. 73, pp. 951 – 964.

study reveals substantial promotion (40% of the mice with tumors) with realistic concentrations of glyphosate as compared to that of applicators using HED methodology.

- **Latency of non-Hodgkin's Lymphoma**: The compilation of peer-reviewed latency estimates presented herein (see **Table 19**) demonstrates latency intervals within a typical range of 2 to 25 years. Based upon the study findings, the weight of available evidence indicates that a minimum latency interval of 2 to 25 years is required and is scientifically reliable. Mr. Cervantes' clinical NHL diagnosis and latency of approximately **22 years** is within the normal latency range. It is noteworthy that studies by Eriksson, et al., (2008) found an increased effect estimate for subjects with more than 10 years of glyphosate exposure prior to NHL diagnosis, thus favoring a longer latency interval.

- **Scope of Exposure in Comparison to Epidemiological Studies:** Mr. Cervantes' exposure doses in units of duration and frequency were compared to the reference doses in six epidemiological studies. The studies included Eriksson, et al.[366], McDuffie, et al.[367], Leon, et al., 2019, [368] (study combining data from >300,000 farmers or agricultural workers from France, Norway and the USA), the Agricultural Health Study (AHS), Pahwa, M. et al., 2019 [369] and Zhang, L., et al., (2019). [370]

  The Zhang, et al., study is a meta-analysis design that included the most recent update of the Agricultural Health Study cohort published in 2018 along with five case-control studies. Mr. Cervantes' calculated 8-hour, time-weighted midpoint exposure dose (***187 exposure-days***) was consistently in excess of the threshold exposure doses

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[366] Eriksson, M., et al., "Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis," 2008, International Journal Cancer, Vol.123, pp. 1657 – 1663.

[367] McDuffie H., et al., "Non-Hodgkin's Lymphoma and Specific Pesticide Exposures in Men: Cross-Canada Study of Pesticides and Health," 2001, Cancer Epidemiology, Biomarkers & Prevention, Vol.10, pp. 1155 – 1163.

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[370] Zhang et al., "Exposure to Glyphosate-Based Herbicides and Risk for Non-Hodgkin Lymphoma: A Meta- Analysis and Supporting Evidence," 2019, Mutation Research-Reviews in Mutation Research https://doi.org/10.1016/j.mrrev.2019.02.001

reported within all of the studies revealing statistically significant increased rates of NHL.[371]

Summary and Conclusions

My toxicological assessment of the current matter includes assessment of the human epidemiological studies discussed above, the dose/response (biological gradient), strength of association, consistency and coherence of the six primary studies and the studies of various chemical formulants and additives found in the Roundup product as well as experimental evidence including absorption, distribution (*i.e.,* measurement in bone marrow), metabolism and excretion (ADME) and the various mechanisms of carcinogenesis (including genotoxicity, impairment of DNA repair mechanisms and promotion). Additionally, I have focused on dermal absorption, the manner and degree to which Roundup penetrates the skin, the lack of adequate PPE and additive toxicological effects of POEA and POEA derivatives used in the product. I have carefully examined Mr. Cervantes' history for any potential toxicological factors and have found none except cancer within the first generation of relatives.

Based on the findings of applicable studies as noted herein and on the basis of sufficient exposure, dose, duration and episodic exposures to Roundup® consistent with the human exposure durations in the epidemiological studies, it is my opinion, to reasonable toxicological certainty, that Mr. Cervantes' exposure to Roundup® is a substantial contributing factor to his development and subsequent diagnosis of diffuse large B-cell lymphoma.

William R. Sawyer, Ph.D.
Chief Toxicologist

[371] The Leon study was of borderline statistical significance (@ 95% confidence interval, but not exceeding it).

Appendix A: Documents

Previously Disclosed Documents (Jimenez report and prior)

1. All previous deposition testimony, trial testimony, and reports given by Dr. Sawyer in Johnson v. Monsanto, Hall v. Monsanto, Stevick v. Monsanto, Pilliod v. Monsanto, Cazier v. Monsanto, Lamb/Cohen, et al., v. Monsanto, Adams, et al., v. Monsanto, Winston, et al., v. Monsanto, Gordon v. Monsanto, Giglio v. Monsanto, Caballero v. Monsanto, Dickey, et al., v. Monsanto, Harris/Hernandez v. Monsanto, Wade, et al., v. Monsanto, Alvarez v. Monsanto, Priest v. Monsanto, Bognar, et al., v. Monsanto, Kane, et al., v. Monsanto, Seitz, et al., v. Monsanto, Hardy et al., v. Monsanto, Whitby et al., v. Monsanto, Seidl et al., v. Monsanto and Jimenez v. Monsanto.
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New Materials Reviewed Specific to Gerard Francis Cervantes

451. Images of Roundup Labels from Mr. Cervantes (PDFs)

452. Cervantes, Gerard - Pathology (new 11-30-20)

453. Cervantes, Gerard - Advocate Medical Records

454. Cervantes, Gerard - Cervantes Exhibits

455. Cervantes, Gerard - Deposition Transcript

456. Cervantes, Gerard - Medical Summary

457. Cervantes, Gerard – Plaintiff Fact Sheet