The Low Down on Roundup

Part II: Regulatory and Human Health Milestones
1970-2000

Developed By:

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1970s: Roundup Hits the Market

The first regulatory actions on glyphosate occurred in the 1970s, leading to the commercial birth of Roundup in 1974.

- 1973- Early glyphosate toxicology studies conducted


- 1974 - Monsanto granted U.S. patent (# 3,799,758) for glyphosate herbicide (N-Phosphonomethyl-glycine)

1974: Roundup is Registered

Early Roundup labels covered mostly non-agricultural uses, like treating rights of way, industrial yards, and other non-crop areas.

Because glyphosate kills all growing plants, it could not be directly sprayed on crops.

1975: Tolerances Set at 0.1 ppm

Initial tolerances were set at 0.1 parts per million (ppm) to cover residues of glyphosate soybeans and other crop grains, and 0.2 ppm for forage (grasses and soybean hay/straw). (EPA, 1975)

Food crop tolerances were needed to cover residues resulting from glyphosate spray drift, or early-season, pre-emergence applications.
1977: Shaky Tox Base for Tolerances

July 1, 1977 document reports EPA acting on 5 Monsanto tolerance petitions covering several crops (EPA, 1977).

Tox Branch lists 8 studies supporting the tolerances -- all done by the discredited lab IBT, and all either dismissed as fraudulent or highly questionable. So...

1977, Subtopic:

...for almost a decade, tolerances covering glyphosate residues in food were supported by no valid tox studies.

1979: Glyphosate ADI/RfD Set 0.05 mg/kg/day

EPA sets the glyphosate Acceptable Daily Intake (ADI) at 0.05 mg/kg/day, 35-times lower than the current chronic Reference Dose.

The 0.05 ADI is based on a 2-year rat feeding study with a NOAEL of 5 mg/kg/day and a 100-fold safety factor (i.e., 5/100 = 0.05). (EPA, 1979)
1980s: Acceptable Dose Increases

The basis for setting glyphosate’s ADI/RfD was “under discussion” throughout the 1980s.

EPA risk assessments showed that existing glyphosate uses accounted for one-third or more of the maximum, allowable daily intake for children.

Bottom line – without a higher RfD, there would be little room to increase glyphosate use on food crops.

1982: Monsanto Dodges a Bullet

EPA reviews a new 2-year rat study commissioned by Monsanto, done to replace an earlier study by IBT deemed “invalid” because of fraud.

The NOAEL for this study is 3 mg/kg/day, which would support a cRfD of 0.3 mg/kg/day (EPA, 1982a).

This is the study European regulatory authorities use as the basis of the EU cRfD of 0.3 mg/kg/day.

1982, Subtopic:

Back at the ranch in the U.S., Monsanto argues to EPA that its new study is flawed and promises to replace it.

In the interim, EPA quietly raised the cRfD to 0.1 mg/kg/day, double the existing 0.05 mg/kg/day, as this document from 1982 shows (EPA, 1982b).

Please be in touch if you know why, or have such a document.

Another memo from the Toxicology Branch on 4/3/85 summarizes the key finding -- "Glyphosate was oncogenic in male mice causing renal tubule adenomas, a rare tumor, in a dose-related manner" (EPA, 1985b).

This EPA determination raises a cluster of new issues...

The Delaney Clause in the Food, Drug, and Cosmetic Act forbids EPA from setting Section 409 food additive tolerances for cancer-causing pesticides. See the 1987 NAS “Delaney Paradox” report here https://www.nap.edu/read/1013/chapter/1

Glyphosate would need several food additive tolerances for its food crop uses to expand.

The renal tubule adenomas in male mice are intensely debated over the course of multiple EPA-Monsanto exchanges.

On April 3, 1985, the very same day EPA classifies glyphosate as a “possible carcinogen” (EPA, 1985b), Monsanto officials arrange for the slides in the mouse study to be sent from the contract lab Bio/dynamics to Dr. Marvin Kuschner, a pathologist Monsanto hired to re-read the slides.
1985-1991, First Subtopic (positive/negative):

Monsanto pressures EPA to reassess the number of tumors in the control (non-treated) group of male mice, after Dr. Kuschner identified one more tumor in the control group -- a finding that changed the study from “positive” for cancer to “negative.” (EPA, 1986)


This re-reading of the control-group slides, and how EPA responded, remains suspect and highly controversial.

1989: Soybean Tolerance Increases to 6 ppm

EPA increases soybean grain tolerance from 6 ppm to 20 ppm, and soybean hay/straw from 15 to 200 ppm. (EPA, 1989).

New tolerance is 200-times higher than the initial soybean tolerance (0.1 ppm) set in 1975.
1989, Subtopic: Pre-Harvest Glyphosate Use

This big jump in the soybean tolerance has nothing to do with higher residues in GE-Roundup Ready soybeans, which would not be sold for 11 years.

The soybean tolerance was raised to cover pre-harvest, desiccation uses of glyphosate. Such uses were common to speed up harvest operations on farms double-cropping wheat and soybeans.

1989-1998: Monsanto Pushes for Higher cRfD

Monsanto urges EPA to increase glyphosate’s cRfD from 0.1 mg/kg/day to 2.0 mg/kg/day – a 20-fold increase.

The increase is needed because of rapidly rising use of glyphosate, and the likelihood of much higher residues in food from pre-harvest desiccation applications and forthcoming GE-RR crops.

1989-1992, First Subtopic (dancers): The Dance

Cancer finding a problem? Re-read the slides.

RfD too low? Convince EPA the study supporting it is flawed, and promise to do a new, better study.

Design and carry out the new study in-house, discover data supporting a higher NOAEL.

Pressure EPA to adjust the cRfD upward, based on the new, “improved” study.

This back-and-forth between Monsanto and EPA plays out several times when regulatory thresholds threaten to curtail new glyphosate uses.

1990s, Stacked Slide (1/2): Big Changes Ahead

Big changes coming – commercial introduction of Roundup Ready (RR) soybeans, cotton, and corn.

RR technology allows post-emergence (after a crop has emerged and is growing) uses of glyphosate, killing weeds but leaving the RR plants unharmed.

1990s, Next Slide (2/2):

Diversification in how and when glyphosate is sprayed lead to many changes in regulatory assessments and benchmarks...

... and huge increases in the acres treated with Roundup.
1990: Soybean Tolerances Increase up to 33-Fold

Once again, the EPA increases a soybean tolerance:

- Soybean Hay - from 6 to 200 ppm

As well as a wheat tolerance:

- Straw - from 0.1 to 40 ppm

1991: Cancer Risk Reclassified

By 1991, Monsanto pressure prevails. EPA reclassifies glyphosate as a Group E carcinogen – “evidence of non-carcinogenicity for humans.”

Unusual Dissent at the EPA

Three of the 18 members of the EPA “Carcinogenicity Peer Review Committee” do not concur with the Committee’s decision to downgrade glyphosate’s cancer classification (EPA, 1991).

1991, Subtopic:

This change in cancer classification allows EPA to approve “food additive” tolerances needed to expand glyphosate use on wheat, soybeans, corn, and other crops...

...and opens the door for GE-Roundup Ready crops that would reach the market in 1996.
1993: EPA Regulatory Review

EPA completes a Reregistration Eligibility Decision (RED) for glyphosate.

The document describes a Monsanto proposal to increase the chronic Reference Dose (cRfD) 20-fold, from 0.1 to 2.0 mg/kg/day.

1993, Subtopic:

The 1993 RED document discusses the proposal to increase the cRfD, but does not officially adopt it.

If accepted, the new cRfD would be based on a short-term rabbit development study from 1980 with a NOEL of 175 mg/kg/day. – This would lead to a cRfD of 1.75 mg/kg/day, which EPA rounded up to 2.0.

1993, Subtopic, Secondary Subtopic:

EPA documents identify several serious problems with the rabbit study, including evidence of adverse effects at the dose level determined to be the NOAEL.

Lower NOAELs in three other studies were not used to set glyphosate’s cRfD.
1994: Ruling on AMPA Regulation

After application, glyphosate is metabolized by plants into aminomethylphosphonic acid, or AMPA, shown to the left.

The Food and Agricultural Organization considers AMPA to be 50% more toxic than glyphosate.

1994, First Subtopic (EPA Logo), Stacked Slide (1/3):

A key March 2, 1994 memo sets the stage for the decision by the EPA Metabolism Committee over whether to continue counting AMPA residues in quantifying glyphosate dietary exposures and setting tolerances.

This will have serious implications on dietary risk from residues of glyphosate and AMPA.

1994, First Subtopic, Next Slide (2/3):

The 3/2/94 memo states – “Monsanto Company has informed the Agency that they have/are developing glyphosate resistant crops which would allow weed control using foliar sprays of glyphosate quite close to harvest. The metabolism of glyphosate in these transgenic crops results in a different ratio of parent compound to AMPA” (EPA, 1994a).
1994, First Subtopic, Next Slide (3/3):

The memo goes on to explain that in non-GE soybeans, the ratio of glyphosate residues to AMPA residues is 9 to 1. In GE-RR soybeans, the ratio “can approach 1 to 1” (EPA, 1994a).

So, dropping AMPA from consideration in setting the glyphosate tolerance for soybeans increases the allowable level of residues by nearly 10-fold.

1994, Second Subtopic ("Science"):

Monsanto residue trials show that in GE- Roundup Ready soybeans, ~56% of the residues remaining after glyphosate application are AMPA, and ~28% are glyphosate (EPA, 1994a).

Even in the face of these data, the EPA Metabolism Committee decided that “AMPA need not be regulated [included in glyphosate residues] regardless of levels observed in foods and feed” (EPA, 1994b).

1996: Food Quality Protection Act Passed

The Food Quality Protection Act (FQPA) was signed into law by Bill Clinton on August 3, 1996.

This seminal legislation was designed to more fully protect pregnant women, infants, and children from the developmental effects of pesticides.
1996, Subtopic, Stacked Slide (1/2): The “Risk Cup”

EPA introduces the concept of the “risk cup” in implementing the FQPA. The volume, or size, of the “risk cup” for a given pesticide is set by the pesticide’s maximum daily exposure, as quantified through the chronic Reference Dose (cRfD).

The more toxic the pesticide, the smaller the allowed “risk cup.”

The FQPA includes a provision requiring EPA to apply an additional 10-fold safety factor when setting cRfDs and evaluating tolerances, to more assuredly protect vulnerable populations (i.e. pregnant women, infants and children). The EPA Administrator can reduce or drop the added safety factor if developmental risks are well characterized, pose little risk, and the agency has solid data to estimate exposures.

1996, Subtopic, Next Slide (2/3):

The EPA has never used its authority under the FQPA to lower the glyphosate chronic Reference Dose, because the agency believes glyphosate reproductive health risks are “well-characterized.”

1996: Tolerances for Wheat and Alfalfa Hay Increase

- Alfalfa Hay - from 0.2 to 200 ppm (EPA, 1996)
- Wheat Straw - from 40 to 85 ppm
- Wheat Grain - from 0.1 to 5 ppm
1997: Corn Tolerances Take a Big Jump

Corn tolerances took a big leap this year to allow for the higher residues found in GE RR corn.

- Corn Stover (the stalks and other remnants after harvest) - from 0.1 to 100 ppm (1,000-fold!!)
- Field Corn Grain - from 0.1 to 1 ppm (EPA, 1997)

1998: RfD Increases 20-Fold to 2.0 mg/kg/day

April 20, 1998 EPA document provides official confirmation that the glyphosate chronic Reference Dose has been increased 20-fold, from 0.1 mg/kg/day to 2.0 mg/kg/day (EPA, 1998).

2000s: Glyphosate Use Surges

Monsanto's work to facilitate friendly regulation pays off, and use of Roundup and other glyphosate-based herbicides surges throughout the decade.

U.S. agricultural glyphosate use almost triples, rising from 79 to 230 million pounds from 2000-2010 (Benbrook, 2016).
2000: Wheat Straw Tolerance from 85 to 100 ppm

EPA grants Monsanto's request to raise the tolerance for wheat straw from 85 to 100 ppm.

This change was needed to cover glyphosate residues in wheat from fields on which glyphosate was used as a desiccant to speed up harvest operations.

The Big Picture, Stacked Slide (1/2):

Glyphosate tolerances increase in leaps and bounds from 1975, rising in some cases 1000 to 2000 times.

Increases pave the way for the approval of new ways to use glyphosate, and make possible the introduction of GE-Roundup Ready crops.

The Big Picture, Next Slide (2/2): Glyphosate’s “Risk Cup” Runneth Over – So Make It Bigger!

As EPA approved more uses of glyphosate in the 1990s – and especially uses later in the crop growing season -- tolerances had to be raised to cover unavoidable residues.

More and higher residues led to higher estimates of dietary exposure, and less “room” in the glyphosate risk cup.

By the time GE-RR crops hit the market, there was not enough room in glyphosate’s “risk cup” to support such significant new uses.

Monsanto overcame this problem by convincing EPA to increase glyphosate’s cRfD 20-fold based on an old (1980) and flawed study.
In 2009, EPA published the Final Work Plan for the latest 15-year Registration Review for glyphosate.

The agency describes a 6 year process to assess the ecological and human health risks of glyphosate, set to be completed in 2015 (EPA, 2009).

However, glyphosate re-registration has dragged on, and as of mid-2017 a ruling has yet to be finalized.

Ongoing debate over the cancer-causing potential of glyphosate is the main culprit for the delay. See Part V of the Lowdown on Roundup for more Human Health impacts.

Stay tuned as this important regulatory process unfolds.

**Key Acronyms and Definitions:**

**AMPA** - Aminomethylphosphonic acid is the main metabolite that glyphosate breaks down to in plants, food, people, and the soil.

**cRfD** - Chronic Reference Dose, a measure of the maximum level of a pesticide that a person can be exposed to in a day, without exceeding the EPA’s “level of concern.” Expressed as milligrams of pesticide per kilogram of bodyweight per day (mg/kg/day). Sometimes also called an Acceptable Daily Intake (ADI), or just RfD.

**FQPA** - Food Quality Protection Act, a federal law passed in 1996 that changed the way pesticides are regulated by the EPA, including the setting of tolerances.
the FQPA includes a provision requiring the EPA to apply an additional 10-fold safety factor when setting chronic Reference Doses and evaluating tolerances, to more assuredly protect vulnerable populations including pregnant women, infants and children. The law allows the EPA Administrator to reduce or drop the added, 10-fold safety factor if he/she concludes that developmental risks are well characterized, pose little risk, and the agency has solid data to estimate exposures.

NOAEL - No Observable Adverse Effect Level, the next dose level down from the lowest level at which an adverse biologically impact is observed in a laboratory study. Sometimes reported as the NOEL (No Observable Effect Level).

Project Sources:

Our project team combed through a mountain of EPA documents and herbicide use data to create these timelines, and we are sharing it all with you!

Reference List (PDF):

Online Bibliography for Part II:
http://cehn-healthykids.org/bibliography-tag/lowdown-part2/

Sources, Subtopic: Want More?

Each regulatory milestone and decision in Part II is linked to one or more EPA document(s). A more detailed explanation of the content and importance of these key EPA documents can be found at the link below:

One more note on source documentation:

While we have done our best to find the most accurate source documents, the EPA online records system is a complex maze of regulatory memos, reports, and policies.

If you have a document that clarifies any of the points on our timeline, please share it with us at charlesbenbrook@gmail.com.